Available online on www.ijtpr.com
International Journal of Toxicological and Pharmacological Research 2010; 2(3): 77-80
ISSN: 0975-5160

Research Article

Influence of Lansoprazole on Anti-diabetic Effect of Pioglitazone in Normal Rats, Diabetic Rats and Normal Rabbits

Suresh D. K[1]*, Loya P. J[1], Kature D. V[1], Gopala krishna C. H[1], Khalid M. D[1], Jyoti G. J[1].

[1] *Department of Pharmacology, Luqman College of Pharmacy, Post Box No- 87,Old Jewargi road, Behind P & T colony, Gulbarga-585102, Karnataka, India.*

ABSTRACT

The present study was carried out to evaluate the drug-drug interaction between anti-diabetic drug and anti-ulcer drug. Interaction of pioglitazone, thiazolidinedione anti-diabetic drug with lansoprazole (anti-ulcer drug) was evaluated in normal, streptozotocin induced diabetic rats and in normal rabbits. The blood samples were collected from normal, diabetic rats and in normal rabbits at different time interval upto 24hrs and blood glucose was estimated by GOD/POD method. Lansoprazole (30mg/kg p.o.) pretreatment has significantly enhance the peak hypoglycemic effect from 49.88 ± 2.90% to 58.75 ± 1.43% in normal rats and significantly enhanced the peak anti-diabetic effect from 52.40 ± 1.37% to 64.33 ± 1.69% in diabetic rats. Similarly pretreatment with lansoprazole (100mg/kg p.o.) has also significantly enhance the peak hypoglycemic effect from 35.89 ± 1.91% to 45.31 ± 0.56%. Duration of anti-diabetic effect was raised from more than 24hrs. this study indicates that therapeutic drug monitoring has to be required to re-adjust the therapeutic dose of lansoprazole and pioglitazone when they are used concomitantly.

KEY WORDS: - Lansoprazole, pioglitazone, streptozotocin, anti-diabetic activity.

INTRODUCTION

Drug interaction is the modification of the effect of one drug (object drug) by the prior or concomitant administration of another drug (precipitant drug). Drug interaction may either enhance or diminish the intended effect of one or both drugs. It may modify the diagnostic, preventive or therapeutic activity of either drug[1]. In poly pharmacy, it is important to determine the incidence of drug interactions, which serious implications, in hospitalized patients. In addition, it is also important to find out agents that are most likely to produce hazardous interactions[2]. As per survey, the incidence of drug-drug interaction ranges from 3 to 5% in patients taking a few drugs to 20% in patients receiving many drugs. According to a report that, the drug interaction may be fourth to sixth leading cause for death in United States[3, 4].

Diabetes mellitus – a metabolic disorder characterized elevated blood glucose levels requires lifelong treatment. Diabetic patients may also be affected with many other diseases like peptic ulcer, hypertension and fungal infections, which require prolong treatment [5].

There are reports that several patients suffering from diabetes, are prone to peptic ulcer infections[6]. In such cases Antiulcer agent like omeprazole, pentaprazole, lansoprazole, ranitidine etc and Thiazolidinedione (Antidiabetic agents) like Pioglitazone is administered concomitantly.

There are reports that lansoprazole is known to inhibit

Table no 1: Percentage decrease in blood glucose levels at different time intervals in normal rats.

Time in hrs	Lansoprazole (30mg/kg p.o)	Pioglitazone (10mg/kg p.o.)	Lansoprazole (30mg/kg p.o, 7days) + Pioglitazone (10mg/kg p.o.)
Fasting	----	----	----
1.0	-0.75 ± 1.76	7.02 ± 3.32	11.73 ± 1.76
2.0	2.18 ± 1.0	19.03 ± 3.39	21.81 ± 1.94
4.0	-0.78 ± 0.86	30.58 ± 3.12	39.66 ± 0.08*
8.0	-0.82 ± 1.23	49.88 ± 2.90	58.75 ± 1.43*
12.0	1.61 ± 0.65	32.86 ± 1.82	36.45 ± 5.20*
18.0	1.05 ± 0.81	21.84 ± 1.89	34.90 ± 3.14**
24.0	-0.34 ± 1.0	15.92 ± 2.89	32.07 ± 0.74***

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

*Author for correspondence: didagi_suresh@yahoo.co.in

cytochrome P-450 enzyme system[7]. Therefore the present study was conducted on normal, diabetic rats and normal rabbits to assess the influence of lansoprazole pretreatment on the Antidiabetic effects of thiazolidinedione like Pioglitazone.

MATERIALS AND METHODS

Animals

Study was conducted on normal, diabetic rats and normal rabbits (wistar strain) of either sex, weight range 150-200g in rats, 1.5-1.8 kg in rabbits. The animals were produced from Mahavir enterprises Hyderabad. They were housed under standard conditions (temperature of 28 ± 2°C and 50 ± 2% relative humidity with 12 hr light/dark cycle) and provided with water *ad libitum.* Prior approval by institutional ethics committee (reg.no: 146/1999/CPCSEA) was obtained for conduction of experiments. The study was conducted in the Department of Pharmacology of Luqman College of pharmacy, Gulbarga between 2009 and 2010.

Drugs

Lansoprazole were obtained from Lee pharma Ltd Hyderabad. Pioglitazone obtained from Cadila Pharma pvt.Ltd. Ahmedabad. Pioglitazone (10mg/kg p.o.) and lansoprazole (30mg/kg p.o.) suspensions were prepared using 2% w/v gum acacia as suspending agent.

Experimental Procedure

Induction of Diabetes mellitus

Diabetes was induced in the rats by administering streptozotocin (50mg/kg) intraperitoneally into the 24hr fasted rats[8,9]. Blood samples were collected after 24hrs 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 7 days. From this it was confirmed that diabetes was induced in 24 hrs and stabilized within 7days. These animals were used for further studies. The normal, diabetic rats and normal rabbits were marked conveniently and distributed randomly into three groups of 6 animals each separately. All the animals were over night fasted with water *ad libitum.* The animals in group-1 received lansoprazole (30mg/kg p.o.) for rats, (100mg/kg p.o.) for rabbits respectively. Animals in the group-2 received pioglitazone (10mg/kg p.o.) for rats, (25mg/kg p.o.) for rabbits respectively. Group-3 received lansoprazole (30mg/kg p.o.) for 7days on the 7th day, 6 hrs after administration of lansoprazole, the animals were fasted for 14hrs. on the 8th day, lansoprazole was given as usual. One hour after the treatment, animals of group-3 received Pioglitazone (10mg/kg p.o.). incase of rabbits group-3 received lansoprazole (100mg/kg p.o.) for 7days. On the 7th day, 6hours after administration of lansoprazole, the animals were fasted for 14hours. On the 8th day, lansoprazole was given as usual. One hour after the treatment, animals of group-3 received Pioglitazone (25mg/kg p.o.). blood samples were collected thereafter at above mentioned intervals and glucose levels were estimated. The percentage blood glucose reductions at various time intervals were calculated and compiled (table 1,2,3).

Statistical analysis:

The data were analyzed by student 't" test. P values lower than 0.05 were considered as statistically significant.

RESULTS

It is evident from table no 1 and 2 that treatment with lansoprazole alone did not alter the blood glucose levels in normal and diabetic rats. However, lansoprazole pretreatment (30mg/kg p.o.) has significantly enhance peak hypoglycemic effect from 49.88 ± 2.90% at 8th hr to 58.75 ± 1.43% at 8th hr. Lansoprazole pretreatment (30mg/kg p.o.) has significantly enhance peak anti-diabetic effect from 52.40 ± 1.37% at 8th hr to 64.33 ± 1.69% at 8th hr. and duration of hypoglycemic and anti-diabetic effect was raised for more than 24hrs.

Similarly pretreatment with lansoprazole (100mg/kg p.o.). has also significantly enhanced peak hypoglycemic effect from 35.89 ± 1.91% to 45.31 ± 0.56% at 12th hr duration of hypoglycemic effect was raised for more than 24hrs.

DISCUSSION

Diabetes mellitus is a chronic metabolic disorder requiring lifelong treatment. Peptic ulcer also requires treatment for a prolonged period. If a patient is suffers from Diabetes mellitus as well as peptic ulcer, he has to use Antidiabetic drugs such as Thiazolidinedione

Table no 2: Percentage decrease in blood glucose levels at different time intervals in diabetic rats.

Time in hrs	Lansoprazole (30mg/kg p.o)	Pioglitazone (10mg/kg p.o.)	Lansoprazole (30mg/kg p.o, 7days) + Pioglitazone (10mg/kg p.o.)
Fasting	----	----	----
1.0	0.256 ± 0.20	13.92 ± 0.53	12.46 ± 1.54
2.0	0.384 ± 1.07	33.57 ± 4.43	27.40 ± 2.52
4.0	0.295 ± 0.14	46.58 ± 1.75	56.17 ± 1.77**
8.0	1.943 ± 0.67	52.40 ± 1.37	64.33 ± 1.69**
12.0	0.04 ± 1.53	30.71 ± 2.97	55.94 ± 3.06***
18.0	2.69 ± 1.28	23.78 ± 1.70	31.70 ± 3.94***
24.0	4.604 ± 2.02	5.37 ± 1.20	20.41 ± 1.34***

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

like Pioglitazone and Antiulcer agent like lansoprazole. In such instances, there is a possibility of occurrence of drug interactions. Our pilot study has indicated that drug interactions occur when lansoprazole and Pioglitazone are administered concomitantly at therapeutic doses. However, the therapeutic dose was found to influence the Antidiabetic effect significantly.

For the assessment of the potentiation of Antidiabetic 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 [5].

Since lansoprazole (30mg/kg p.o.) *perse* did not influenced the blood glucose levels and thus the possibility of occurrence of pharmacokinetic interaction can be ruled out. In our study, pretreatment with lansoprazole (30mg/kg p.o.) altered the onset of action of Thiazolidinediones, where onset of action, peak effect and duration of Antidiabetic effect induced by Thiazolidinedione were significantly enhanced. This suggests that lansoprazole retards the metabolism of these Antidiabetic drugs by inhibiting the enzymes responsible for their metabolism. There are reports that Pioglitazone is mainly metabolized by CYP2C8, CYP2C9 and CYP3A4[5,10-11]. Reports also indicate that lansoprazole is a weak inhibitor of CYP2C8 and CYP3A4[11-12]. It is evident from the results that the therapeutic dose of lansoprazole enhanced the Antidiabetic effect of the Pioglitazone. This may be due to weak inhibitory effect of lansoprazole on CYP2C8 and CYP3A4[12]. Further studies are undertaken to establish the influence of lansoprazole pretreatment on the pharmacokinetic parameters of Thiazolidinediones.

Our studies in normal, diabetic rats and normal rabbits suggested that drug interaction occurs between lansoprazole and Thiazolidinediones when they used concomitantly in pathophysiological conditions like Diabetes mellitus at very high dose.

In this present study, indicates clearly that during the concomitant administration of thiazolidinediones and lansoprazole at therapeutic doses, the dose and frequency of administration of Thiazolidinediones need to be readjusted. Simultaneously blood glucose levels are monitored during treatment period as precautionary measure so as to avoid severe hypoglycemia.

CONCLUSION

The present study concluded that, during simultaneous treatment of diabetes mellitus with peptic ulcer infections and therapeutic dose of Thiazolidinediones and lansoprazole do interact. Therefore it is necessary to adopt therapeutic drug monitoring so as to readjust dose and frequency of administration of these drugs, when they are used concomitantly to avoid the patients from severe hypoglycemia.

ACKNOWLEDGEMENTS:

The authors are thankful to the principal Dr. Syed Sanaullah for their encouragement and support

REFERENCES

1. Kohler GI et al. Elements of Clinical Pharmacy 1st Ed. BS Shah Prakashan

Table no 3: Percentage decrease in blood glucose levels at different time intervals in normal rabbits.

Time in hrs	Lansoprazole (100mg/kg p.o)	Pioglitazone (25mg/kg p.o.)	Lansoprazole (100mg/kg p.o, 7days) + Pioglitazone (25mg/kg p.o.)
Fasting	----	----	----
1.0	-0.39 ± 0.63	8.10 ± 1.79	3.44 ± 1.73
2.0	-0.97 ± 0.84	16.80 ± 2.66	17.35 ± 1.66
4.0	0.38 ± 0.51	26.31 ± 1.80	33.11 ± 1.04**
8.0	-2.11 ± 0.56	28.62 ± 1.45	40.22 ± 1.71***
12.0	-1.27 ± 1.16	35.89 ± 1.91	45.31 ± 0.56***
18.0	-0.45 ± 0.56	26.32 ± 1.68	41.53 ± 1.34***
24.0	0.23 ± 0.10	8.29 ± 2.34	38.96 ± 1.34***

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

Ahmedabad; 2004; 135-48.
2. Sunilkumar B, Lucia P, Miglani BD. Possible drug interactions in hospitalized patients. The Ind J Hos Pharm 1998; 91-93.
3. Alan S, Nies, Stephen, Spielberg P. Principles of therapeutics: Goodman and Gilman's the pharmacological basis of therapeutics. 10th Ed. Megraw Hill, NewYork; 2001;45-65.
4. Yuan R et al. In vitro studies; experience of the food and drug administration. Clin. Pharmacol. Ther.1999; 66:9-15.
5. Suresh J, Ramchandra SS, Kharya MD. Influence of Itraconazole on Antidiabetic effect of Thiazolidinedione in Diabetic rats. Int J pharma and pharmaceutical science 2009; 1:119-24.
6. 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.
7. Roux A, Naline E, Molinier P, Dellatolas F, Lemaire M. Effect of Lansoprazole and omeprazole on the metabolism of theophylline and antipyrine in man. Eur J Drug Metab Pharmacokinet 1993; 18:125.
8. Kavalali G, Tuncel H, Goksel S, Hatemi HH. Hypoglycaemic activity of *Urtica pilulifera* in streptozotocin-diabetic rats. Journal of Ethnopharmacology. 2003; 84:241-45.
9. Sevugan A, Subramanian K, Balamuthu K, Abdul BAA, Mohammed AA. Antidiabetic activity of leaf and callus extracts of *Aegle marmelos* in rabbit. Science Asia 2008;34:317-21.
10. Prasad P Shitole, Sachin L Badole, Subhash L Bodhankar, Mohan V, Sunil Bhaskaran. Anti-hyperglycaemic activity of IND and its interaction with glyburide and Pioglitazone in alloxan induced diabetic mice. Int J Diabetes and Metabolism 2009; 17:21-26.
11. Shannon F Manzi, Michael Shannon. Drud iteractions – a review. Clinical Pediatric Emergency Medicine 2005.
12. Rajendra SV, Raghuveer Gupta PS, Joshi VG, Anand Kumar Y, Venkat Rao N, et al. Influence of Lansoprazole on hypoglycaemic activity of oral Antidiabetic agents in healthy albino rats. Acta Pharmaceutical Turcica 2004; 46: 95-99.