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INFLUENCE OF FLUCONAZOLE ON HYPOGLYCAEMIC ACTIVITY OF ORAL ANTIDIABETIC AGENTS IN HEALTHY ALBINO RABBITS

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ABSTRACT

The influence of fluconazole pretreatment for seven days on the hypoglycaemic effect of rosiglitazone (720 µg/kg, p.o) and pioglitazone (10 mg/kg, p.o) was studied. This study was conducted on healthy albino rabbits of either sex, randomly distributed into 2 different groups. The two groups were pretreated with fluconazole (400 mg/kg, p.o) in 2%w/v gum acacia suspension for seven days. On eighth day rosiglitazone and pioglitazone were administered to respective groups one hour after fluconazole treatment. Blood samples were collected from marginal ear vein at time intervals of 0, 1, 2, 4, 8, 12, 18, and 24 hours and plasma glucose levels were estimated by using GOD/POD method. The study indicated that fluconazole (at therapeutic dose) pretreatment has enhanced the hypoglycaemic effect of rosiglitazone and pioglitazone significantly. Hence it is suggested that during the concomitant usage of fluconazole and thiazolidinediones (rosiglitazone and pioglitazone), the therapeutic drug monitoring is essential and may also require readjusting the dose and frequency of administration of thiazolidinediones (rosiglitazone and pioglitazone).

KEYWORDS: Fluconazole; Rosiglitazone; Pioglitazone; Hypoglycaemic activity.

INTRODUCTION

Many patients, especially the elderly, are treated continuously with one or more drugs for chronic diseases such as hypertension, diabetes mellitus, heart failure, osteoarthritis, and so on. The potential for drug interactions is therefore, substantial and 'polypharmacy' is an important factor to consider when prescribing in this group (1). According to reports, the incidence of interaction ranges up to 20% in patients receiving more than 10 drugs (2). It is the fourth to sixth leading cause for death in United States (3, 4). 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 fungal infections, peptic ulcers, hypertension etc. There are several patients who are suffering with both diabetes and fungal infection. In such patients anti-fungal agents like fluconazole, itraconazole etc. and thiazolidinediones like rosiglitazone, pioglitazone are administered concomitantly. There are reports that fluconazole is known to inhibit Cytochrome P-450 enzyme system (5), hence there is a possibility of occurrence of pharmacokinetic type of drug interactions with concomitantly used drugs. Pioglitazone and rosiglitazone are metabolized by Cytochrome P-450 enzyme system (6, 7). Therefore the present study was conducted in healthy albino rabbits to assess the influence of fluconazole pretreatment on the hypoglycaemia induced by thiazolidinediones (rosiglitazone and pioglitazone).

MATERIALS AND METHODS

Animals

The study was conducted on healthy albino rabbits (weighing 1.5-2.0 kg of either sex). The animals were randomly distributed into 2 different groups, each group consisting of 3 animals. Albino rabbits were procured from Sainath agencies, musheerabad, Hyderabad. Prior approval by institutional ethics committee was obtained for conduction of experiments (1230/a/08/CPCSEA). The animals were kept in colony cages at standard husbandry conditions.

Drugs: Pioglitazone and Rosiglitazone were obtained from Micro Labs Ltd., Bangalore and fluconazole was obtained from Ipca Labs Ltd.Mumbai.

Preparation of drug for treatment Pioglitazone (10mg/Kg, p.o.), Rosiglitazone (720µg/kg, p.o) Fluconazole (400mg/kg, p.o for 7 days) suspensions were prepared by using 2%w/v gum acacia as a suspending agent.

EXPERIMENTAL PROCEDURE

Healthy albino rabbits were marked conveniently and randomly distributed into two groups of 3 animals in each group. All the animals were fasted for 12 hours with water *ad libitum*. The animals in groups I received suspension of pioglitazone 10 mg/kg and the animals in the groups II received suspension of rosiglitazone 720 µg/kg through oral route. Blood samples were collected at 0.0, 1.0, 2.0, 4.0, 8.0, 12.0, 18.0, 24.0 hours from all the two groups by marginal ear vein in healthy albino rabbits. Blood glucose levels were estimated by GOD/POD method (8) and expressed as mg/100 ml of blood. In the next phase of the experiment, the animals of groups I and II received fluconazole 400 mg/Kg, p.o. for seven days. On the 7^{th} day, 6 hours after administration of fluconazole, the animals were fasted for 12 hours. On the 8^{th} day, fluconazole was given as usual. One hour after the treatment, animals of group I received pioglitazone and group II received rosiglitazone. 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 I.

STATISTICAL ANALYSIS

The data were analysed by using Student t-test (Student Newman Kleus test). P values lower than 0.05 were considered as statistically significant.

RESULTS AND DISCUSSION

For the assessment of the potentiation of hypoglycaemia, the following parameters were considered such as onset of action, (time taken to reduce minimum of 15% reduction in blood glucose levels), peak effect and duration of hypoglycaemia (duration in which minimum of 15% reduction in blood glucose levels are maintained). It is evident from the table I that, fluconazole pretreatment i.e. 400 mg/kg has not significantly altered the onset of hypoglycaemia but significantly enhanced peak hypoglycaemia from 30.32 ± 1.03 % to 38.20 ± 0.52 % after treatment at the 8^{th} hours and duration of hypoglycaemia was raised from 16 hrs to more than 22 hrs after treatment induced by pioglitazone. Whereas preatreatment of fluconazole (400mg/kg) has not significantly altered the onset of hypoglycaemia but enhanced peak hypoglycaemia from 38.89 ± 1.29 % to 43.72 ± 1.21% after treatment induced by rosiglitazone. Duration of hypoglycaemia was not enhanced. Diabetes mellitus is a chronic metabolic disorder which requires treatment for lifelong. Fungal infections are more prone to develop in diabetic individuals. If a patient is suffering with diabetes mellitus and fungal infection, we may have to use antidiabetic drugs such as thiazolidinediones and

antifungals like fluconazole respectively. In such situations, there is a possibility of drug interactions. Since fluconazole perse did not influenced the blood glucose levels and is used to asses the interaction with thiazolidinediones. There are reports that thiazolidinediones are metabolized by CYP3A4, CYP2C8 and CYP2C9 (9, 10). Reports also indicate that fluconazole is a inhibitor of CYP3A4, CYP2C9, CYP2C19 (11, 12). In our study pretreatment with fluconazole did not altered the onset of action of thiazolidinediones, however peak effect and duration of hypoglycaemia induced by thiazolidinediones are significantly enhanced. These findings suggest that fluconazole has not influenced the absorption phase of thiazolidinediones. Fluconazole pretreatment has increased the peak effect and duration of action of thiazolidinediones, this suggest that fluconazole has retarded their metabolism by inhibiting the enzymes responsible for their metabolism. Further studies are undertaken to establish the influence of fluconazole pretreatment on the pharmacokinetic parameters of thiazolidinediones. In the present study, results indicate that during the concomitant administration of thiazolidinediones and fluconazole, the dose and frequency of administration of thiazolidinediones are to be readjusted. In addition, monitoring of regular blood glucose levels during that period is essential to avoid the complications of hypoglycaemia. Our studies in healthy albino rabbits suggested that drug-drug interaction occurs between fluconazole and thiazolidinediones, when they are used concomitantly in healthy conditions.

Table No. I Effect of Fluconazole (400mg/kg) on Pioglitazone (10mg/kg) and Rosiglitazone (720µg/kg) induced hypoglycaemia in healthy albino rabbits.

Time in hours	% Blood glucose reduction with pioglitazone before and after fluconazole treatment (400 mg/Kg) in albino rabbits		% Blood glucose reduction with rosiglitazone before and after fluconazole treatment (400 mg/Kg) in albino rabbits	
	Before	After	Before	After
Fasting	-	-	-	-
1.0	7.72±1.11	12.04 ±0.99	9.08±0.31	10.71±0.78
2.0	16.34±0.76	24.94±1.75**	17.26±1.78	18.86±0.50
4.0	25.46±1.67	31.57±1.91*	25.11±0.96	29.09±1.47
8.0	30.32±1.03	38.20±0.52**	38.89±1.29	43.72±1.21**
12.0	20.94±1.56	33.93±0.63***	29.18±1.15	35.2±2.36**
18.0	17.97±1.78	31.02±0.92***	16.61±1.38	19.2±0.70
24.0	8.81±1.46	24.43±1.86***	8.00±0.09	14.00±1.12**

* Significant at $p< 0.05$; ** highly significant at $p<0.01$; *** Very highly significant at $p<0.001$

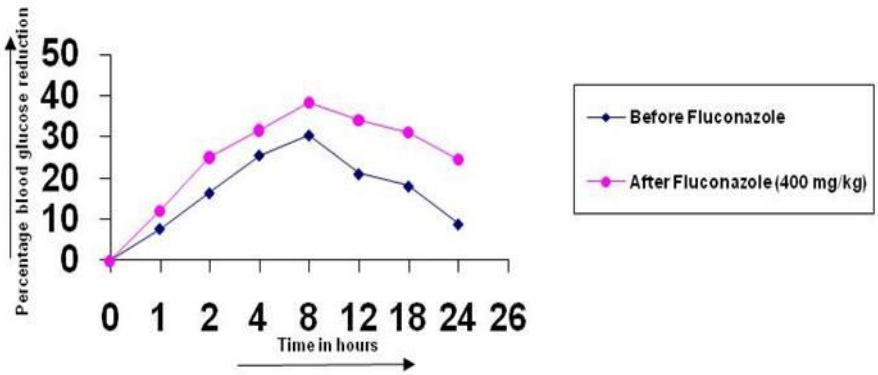

Fig No. 1: Percentage blood glucose reduction with Pioglitazone in healthy albino rabbits

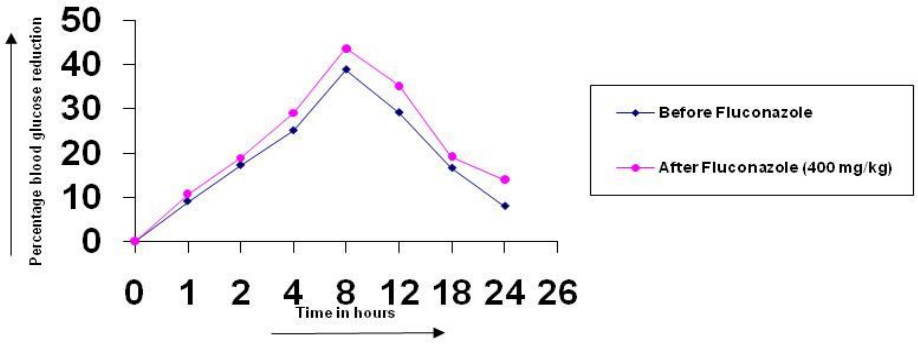

Fig No. 2: Percentage blood glucose reduction with Rosiglitazone in healthy albino rabbits

CONCLUSION

The above observations suggest that the interaction between fluconazole and thiazolidinediones are very intense and it demands the readjustment of dose and frequency of thiazolidinediones when they are used concomitantly. However, these findings are to be further confirmed by determining influence of fluconazole on the pharmacokinetic parameters of thiazolidinediones.

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REFERENCES

1. Rang HP, Dale MM and Ritter JM. Individual variation and drug interaction. Pharmacology 5th Ed. Churchill Livingstone USA (2004): 718.
2. Sunil Kumar Batra, Lucia Panikulam and Miglani BD. Possible drug interactions in hospitalised patients. *The Ind J Hos Pharm.* (1998): 91-93.
3. Alan S, Nies, Stephen and Spielberg P. Principles of therapeutics: Goodman and Gilman's the pharmacological basis of therapeutics. 10th ed. McGraw-Hill, New York (2001): 45-65.
4. Joel G. Hardman, Lee E. Limbird, Alfred Goodman Gilman. Drugs used in Chemotherapy of Protozoal infections, The Pharmacological basis of therapeutics, 10thed. McGraw-Hill Medical Publishing Division. New York (2001):1098.
5. Kunze KL, Wienkers LC, Thummel KE and Trager WF. Inhibition of the human cytochrome P450-dependent metabolism of warfarin by fluconazole in vitro studies. *Drug Metab Dispos.* (1996) 24:414-421.
6. Sahi J, Black CB and Hamilton GA. Comparative effects of thiazolidinediones on *in-vitro* P450 enzyme induction and inhibition. *Drug Metab Dispos.* (2003) 31: 43.
7. Kirchheiner and J. Roots. Effect of genetic polymorphisms in cytochrome P-450 (CYP) and CYP2C8 on the pharmacokinetics of oral antidiabetic drugs: clinical relevance. *Clinical pharmacokinetics.* (2005) 44: 1209-1225.
8. Trinder, P. Determination of Glucose in Blood Using Glucose Oxidase with an alternative oxygen acceptor, *Ann. Clin. Biochem.* (1969)6: 24-25.
9. Lebovitz HE. Differentiating members of the thiazolidinedione class: a focus on safety, *Diabetes Metab Res Rev.* (2002)18: S23-9.
10. Park JY, Kim KA, Shin JG and Lee KY. Effect of ketoconazole on the pharmacokinetics of rosiglitazone in healthy subjects. *Br-J-Clin-Pharmacol.*(2004) 58: 397-402.
11. Venkatakrishnan K, Von-Moltke LL and Greenblatt DJ. Effects of antifungal agents on oxidative drug metabolism clinical relevance. *Clinical pharmacokinetics.* (2000)38: 111-80.
12. Kaukonen KM, Olkkola KT and Neuvonen PJ. Fluconazole but not itraconazole decreases the metabolism of losartan to E-3174. *Eur J Clin Pharmacol.* (1998)53: 445-449.