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Research article

INFLUENCE OF ITRACONAZOLE ON ANTIDIABETIC EFFECT OF THIAZOLIDINEDIONE IN DIABETIC RATS

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ABSTRACT

The present study was carried out to evaluate the drug-drug interaction between antidiabetic drugs and antifungal drugs. Interaction of Pioglitazone and Rosiglitazone the known Thiazolidinedione antidiabetic drugs with Itraconazole (antifungal drug) was evaluated in alloxan induced diabetic rats. The blood samples were collected from diabetic rats at different time interval upto 24hrs and blood glucose was estimated. Itraconazole (18 mg/kg, p.o.) pretreatment has significantly altered the onset of antidiabetic effect of Pioglitazone from 22.70 % to 30.89 % and significantly enhanced the peak antidiabetic effect from 56.21 % to 68.30 %. Similarly pretreatment with Itraconazole (18 mg/kg, p.o) has also significantly altered the onset of antidiabetic effect of Rosiglitazone from 26.74 % to 30.07 % and enhanced the peak antidiabetic effect from 45.08 % to 58.50 %. Duration of antidiabetic effect was raised from more than 24hrs.This study indicates that Therapeutic drug monitoring has to be required to readjust the therapeutic dose of Itraconazole and Thiazolidinedione when they used concomitantly.

Key words: Itraconazole, Pioglitazone, Rosiglitazone, Alloxan, Antidiabetic 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 and frequency of occurrence of drug interactions, which serious implications, in hospitalized patients. In addition, it is also important to findout 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[4].

Diabetes mellitus - a metabolic disorder characterized by 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. There are reports that several patients suffering from diabetes, are prone to fungal infections[5]. In such antifungals agent like Fluconazole, Itraconazole, Miconazole, ketoconazole etc and Thiazolidinedione (Antidiabetic agents) like Pioglitazone or Rosiglitazone are administered concomitantly.

There are reports that Itraconazole is known to inhibit Cytochrome P-450 enzyme system[6,7], hence there is a possibility of occurrence of pharmacokinetic type of drug interactions with concomitantly used drug(s). Pioglitazone or Rosiglitazone are metabolized by Cytochrome P-450 enzyme system[5]. Therefore the present study was conducted on diabetic rats to assess the influence of Itraconazole pretreatment on the antidiabetic effects of Thiazolidinedione like Pioglitazone and Rosiglitazone.

MATERIALS AND METHODS

Animals

Study was conducted on diabetic rats (wistar strain) of either sex, weight range 150-200 g. The animals were procured from Sri Venkateshwara Enterprises, Bangalore. They were housed under standard conditions (temperature of 28 ± 2ºC 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: 157/99/CPCSEA) was obtained for conduction of experiments. The study was conducted in the Department of Pharmacology of S.C.S.College of Pharmacy, Harapanahalli between 2007 and 2008.

Drugs

Pioglitazone and Itraconazole were obtained from Hetro drugs, Hyderabad. Rosiglitazone was obtained from Micro labs, Bangalore. Pioglitazone (10 mg/kg, p.o.), Rosiglitazone (720µg/kg, p.o.) and Itraconazole (18mg/kg, p.o) suspensions were prepared using 2% w/v gum acacia as suspending agent.

Experimental

Induction of diabetes mellitus

Diabetes was induced in the rats by administering alloxan monohydrate (120 mg/kg) intraperitoneally into the 24 hr fasted rats[8,9]. 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 distributed randomly into three groups of 6 animals each. All the animals were over night fasted with water ad libitum. The animals in group-1 received Itraconazole (18mg/kg, p.o.). The animals in the group-2 received Pioglitazone (10 mg/kg, p.o) and group-3 received Rosiglitazone (720 µg/kg, p.o) in acacia suspension.

Blood samples collected at 0.0, 1.0, 2.0, 4.0, 8.0, 12.0, 18.0 and 24.0 hr after treatment by retro-orbital plexus from mild anaesthetized rats. Blood glucose levels were estimated by GOD/POD method[10] and expressed as mg/dl of blood.

In the next phase of the experiment, the animals of group-2 and 3 received Itraconazole 18 mg/kg, p.o. for seven days. On the 7th day, 6 hours after administration of Itraconazole, the animals were fasted for 14 hours. On the 8th day, Itraconazole was given as usual. One hour after the treatment, animals of group-2 received Pioglitazone 10 mg/kg, p.o. and group-3 received Rosiglitazone 720µg/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).

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 no1 that treatment with Itraconazole alone did not alter the blood glucose levels in diabetic rats. However, Itraconazole pretreatment 18 mg/kg, p.o. has significantly altered the onset of antidiabetic effect of Pioglitazone from 22.70 ± 2.30 % to 30.89 ± 2.30 % and significantly enhanced peak antidiabetic effect from 56.21 ± 1.32 % at 8th hr to 68.30 ± 1.44 % at 8th hr and duration of antidiabetic effect was raised for more than 24hrs.

Similarly pretreatment with Itraconazole 10 mg/kg, p.o. has also significantly altered the onset of antidiabetic effect of Rosiglitazone from 26.74 ± 0.55 % to 30.07 ± 0.54 % and enhanced peak antidiabetic effect from 45.08 ± 0.78 % to 58.50 ± 0.28 %. Duration of antidiabetic effect was raised for more than 24hrs.

Table 1 : Percentage decrease in blood glucose levels at different time intervals (Following various treatments in diabetic albino rats)

Percentage reduction in blood glucose concentration (mean ± sem)					
Time in h	**Itraconazole (18mg/kg p.o.)**	**Pioglitazone (10mg/kg, p.o.)**	**Itraconazole (18mg/kg,p.o,7days) + Pioglitazone (10mg/kg, p.o.)**	**Rosiglitazone (720µg/kg, p.o.)**	**Itraconazole (18mg/kg,p.o,7days) + Rosiglitazone (720µg/kg, p.o.)**
Fasting	**----**	**---**	**----**	**---**	**---**
1.0	-0.79 ± 2.62	14.00 ± 1.39	18.41 ± 1.56	13.93 ± 0.38	13.14 ± 1.84
2.0	-1.63 ± 1.43	22.70 ± 2.30	30.89 ± 2.30**	26.74 ± 0.55	30.07 ± 0.54*
4.0	-2.51 ± 1.30	51.99 ± 0.78	62.82 ± 1.36***	32.05 ± 1.00	38.16 ± 0.83***
8.0	-3.92 ± 2.37	56.21 ± 1.32	68.30 ± 1.44***	45.08 ± 0.78	58.50 ± 0.28*
12.0	-2.18 ± 1.90	53.11 ± 0.36	59.64 ± 1.34**	39.37 ± 1.51	43.13 ± 0.73
18.0	-4.50 ± 2.37	36.59 ± 0.49	46.20 ± 1.97***	27.29 ± 1.33	40.69 ± 0.94*
24.0	0.25 ± 2.60	28.85 ± 0.29	36.06 ± 1.59***	25.36 ± 1.41	36.15 ± 0.80*

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

DISCUSSION

Diabetes mellitus is a chronic metabolic disorder requiring lifelong treatment. Fungal infection also requires treatment for a prolonged period. If a patient is suffers from diabetes mellitus as well as fungal infections, he has to use antidiabetic drugs such as Thiazolidinedione like Pioglitazone and Rosiglitazone and antifungal agent like Itraconazole. In such instances, there is a possibility of occurrence of drug interactions. Our pilot study has indicated that drug interactions occur when Itraconazole and Pioglitazone/ Rosiglitazone 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.

Since Itraconazole (18 mg/kg) 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 Itraconazole (18 mg/kg) altered the onset of action of Thiozolidinediones, where onset of action, peak effect and duration of antidiabetic effect induced by Thiazolidinedione were significantly enhanced. This suggests that Itraconazole retards the metabolism of these antidiabetic drugs by inhibiting the enzymes responsible for their metabolism. There are reports that both Pioglitazone and Rosiglitazone are

mainly metabolized by CYP2C8, CYP2C9 and CYP3A4[11-15]. Reports also indicate that Itraconazole is a weak inhibitor of CYP1A2, CYP3A4, CYP2C9, CYP2C19 and CYP2D6[15] . It is evident from the results that the therapeutic dose of Itraconazole enhanced the antidiabetic effect of both the Pioglitazone and Rosiglitazone. This may be due to weak inhibitory effect of Itraconazole on CYP2C9 and CYP3A4[16]. Further studies are undertaken to establish the influence of Itraconazole pretreatment on the pharmacokinetic parameters of Thiazolidinediones.

Our studies in diabetic rats suggested that drug interaction occurs between Itraconazole 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 Itraconazole 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 hypoglycaemia.

CONCLSION

The present study concluded that, during simultaneous treatment of diabetes mellitus with fungal infections and therapeutic dose of Thiazolidinediones and Itraconazole 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 hypoglycaemia.

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