INFLUENCE OF ANTIFUNGAL DRUG ON PIOGLITAZONE: EXPLORING THE PHARMACODYNAMIC RELATIONSHIP

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Abstract

In clinical practice, as there arises several situations, where a diabetic patient receiving pioglitazone need to be administered with an antifungal drug like Ketoconazole. However, the influence of Ketoconazole on anti-diabetic activity of above mentioned drugs has not yet been properly studied and reported. Hence, keeping the possibility of interactions between Ketoconazole and oral anti-diabetic agents in view, the present study was planned to study the influence of Ketoconazole pretreatment on the anti-diabetic activity of oral anti-diabetic agents.

Materials and methods: The whole study was divided into 3 phases.

1. Influence of ketoconazole on blood glucose levels in normal rat and rabbits.
2. Influence of ketoconazole pretreatment (1week) on the hypoglycemic activity of oral anti-diabetic agent in normal rat and rabbits.
3. Influence of ketoconazole pretreatment (1week) on the anti-diabetic activity of oral anti-diabetic agent in streptozotocin induced diabetic rats.

The blood glucose level was estimated with the help of GOD/POD method.

Results and Discussion: Ketoconazole pre-treatment for one week has significantly preponed the onset of hypoglycemia and enhanced the peak hypoglycemic effect of pioglitazone in normal rats/rabbits and diabetic rats. The potentiation of hypoglycaemic effects of pioglitazone by the ketoconazole pretreatment is due to the inhibition of CYP3A4 and CYP2C8 isoenzymes by ketoconazole.

Keywords: Ketoconazole; Pioglitazone; Hypoglycemic; Diabetes Mellitus (DM).

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1. Introduction

Individuals with diabetes mellitus have a greater frequency and severity of infections[1-3]. The reasons for this include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia, as well as diminished vascularization. Many common infections like pneumonia, urinary tract infections and postoperative wound infections are more frequent in the diabetic population, whereas several rare infections like rhinocerebral mucormycosis and emphysematous infections of the gall bladder are seen almost exclusively in the diabetic population. Diabetics are immunocompromised and also susceptible to a number of opportunistic fungal infections[4]. There are documented reports about frequent occurrence of fungal infections[5-8] in diabetics like mucormycosis[9-10], candidiasis[11-12], onychomycosis[13-18] etc. Reports indicate that diabetics are commonly infected with different species of fungi such as Candida, Saccharomyces, Trichosporon, Aspergillus etc. The most frequently detected fungi *are C. albicans, C. glabrata, C. parapsilosis and C. tropicalis*[4,19-25].

To treat fungal infections in diabetic patient ketoconazole is prescribed due to its unique merits like wide spectrum antifungal activity, low cost, usefulness in histoplasmosis and blastomycosis. However, there are plenty of reports indicating that, several co-administered drugs potentiate the hypoglycemic activity of pioglitazone[26]. Ketoconazole is important antifungal agent and reported to inhibit the CYP3A4 and little/less effect on CYP1A2, CYP2C9 and CYP2C8[27]. The oral antidiabetic drug Pioglitazone is metabolized principally by the isoenzyme CYP2C8 and CYP3A4 and to lesser extent by CYP2C9[28,29,30]. Therefore it is possible that the pharmacokinetic type of drug-drug interaction may occur when these drugs are used concomittantly with the drugs that inhibits the cytochrome P-450 enzyme system. Hence, there is every possibility that, drug-drug interaction may occur when oral antidiabetic agent and antifungal drug Ketoconazole used simultaneously.

However, there are no reports available on the drug-drug interaction between oral antidiabetic agents pioglitazone and Ketoconazole. Hence, it is planned to investigate the possible interaction between Ketoconazole and oral antidiabetic agent pioglitazone with respect to blood glucose reduction in normal albino rats, healthy albino rabbits and diabetic rats.

2. Materials and Methods

2.1 Animals

Albino rats (n=6) and albino rabbits (n=4) of either sex weighing between 150-250 gm and 1.5-2.5 kg respectively were selected for the study. They were marked conveniently. The animals were kept in colony cages at ambient temperature of $28^0 \pm 2^0$ C and 45 to 55% relative humidity with a 12 hour light / dark cycle. The animals were fasted for 18 hours before commencing the experiment. During this period, the rats were supplied with water *ad libitum*. The fasting was continued till the completion of the experiment.

2.2 Drugs

Glucose estimation Kit and Autoanalyzer were used in the present study. All the drugs used in this study were administered by suspending separately in 2 % w/v gum acacia suspension in distilled water.

2.3 Induction of diabetes

Adult (9 weeks old) male wistar rats were made diabetic with an intraperitoenal injection of streptozotocin (STZ, 65 mg/kg body weight) dissolved in citrate buffer (0.1 M, pH 4.5). Streptozotocin injected animals exhibited massive glycosuria and hyperglycemia within a few days. Diabetes was confirmed in STZ rats by measuring the fasting blood glucose concentration, 96 hours after the injection with STZ. Albino rats with blood glucose level above 200 mg/dL were considered to be diabetic and were used in this project. Six rats were injected with saline that served as control.

2.4 Method for collection of blood and serum sample

The blood samples were collected from tail vein of rats[31] and from the marginal ear vein of rabbits. The serum was obtained by centrifuging the blood samples for 10minutes at 5000rpm decanting supernatant fluid in to the clean, dry test tube[32-40].

2.5 Estimation of blood glucose

Blood glucose level was estimated with the help of GOD/POD method; which intended for in-vitro quantitative determination of glucose in serum / plasma or cerebrospinal fluid[41-49]. Blood samples were collected at pre-determined time intervals (0, 0.5, 1, 2, 4, 8, 12, 18 and 24 hours) and serum was separated by centrifuging blood samples at 5000 rpm. After adding the reagent the tubes were mixed and incubated for 10 minutes at 37°C or for 15 minutes at room temperature and glucose levels were directly obtained in Erba Mannheim chem -5 plus V_2 autoanalyser.

2.6 Experimental procedure

2.6.1 Influence of ketoconazole on blood glucose levels in normal albino rats

Ketoconazole (3.6 mg/kg p.o. Twice a day) was administered to all the rats for one week. On the 7th day, 6 hours after administration of Ketoconazole, the rats were fasted for 18 hours. On the 8th day, the blood samples were collected after the administration of ketoconazole at pre-determined time intervals.

2.6.2 Effect of ketoconazole pre-treatment on the hypoglycemic activity of pioglitazone in normal albino rats

In the first part of this anti-diabetic study, the healthy rats received suspension of pioglitazone (270 µg/kg) through oral route and blood samples were collected at different time intervals up to 24 hours.

In the next part, all the healthy rats were treated with ketoconazole (3.6 mg/kg p.o. twice a day) for one week. On the 7th day, 6 hours after administration of Ketoconazole, the rats were fasted for 18 hours. On the 8th day blood samples were collected for determining fasting blood glucose levels and ketoconazole (3.6 mg/kg p.o. twice a day) was administered orally to all the animals. After 60minutes, pioglitazone (270µg/ kg) was administered to animals. Blood samples were collected thereafter at different time intervals up to 24 hours.

2.6.3 Influence of ketoconazole on blood glucose levels in normal albino rabbits

Ketoconazole (14 mg/kg p.o. twice a day) was administered orally to all the rabbits for one week. On the 7th day, 6 hours after administration of Ketoconazole, the rabbits were fasted for 18 hours. On the 8th day, blood samples were collected at pre-determined time intervals after the administration of ketoconazole.

2.6.4 Effect of ketoconazole pre-treatment on the hypoglycemic activity of pioglitazone in normal albino rabbits

In the first part of this anti-diabetic study, the healthy rabbits were received suspension of pioglitazone (270µg/kg) through oral route and blood samples were collected at different time intervals up to 24 hours.

In the next part, all the healthy rabbits received suspension of ketoconazole (14 mg/kg p.o. twice a day) for one week. On the 7th day, 6 hours after administration of ketoconazole the rabbits were fasted for 18 hours. On the 8th day, ketoconazole (14 mg/kg p.o. twice a day) was administered orally to the animals. After 60 minutes pioglitazone (270µg/kg) was administered to group. Blood samples were collected thereafter at different time intervals up to 24 hours.

2.6.5 Effect of ketoconazole pre-treatment on the antidiabetic activity of pioglitazone in diabetic rats

In the first part of this anti-diabetic study, the diabetic rats received suspension of pioglitazone (270µg/kg) through oral route and blood samples were collected.

In the next part of this experiment, all the diabetic rats were treated with ketoconazole (3.6 mg/kg p.o. twice a day) for one week. On the 7th day, 6 hours after administration of ketoconazole, the rats were fasted for 18hours. On the 8th day, ketoconazole (3.6 mg/kg p.o. twice a day) was administered orally to all the animals. 60 minutes later, pioglitazone (270µg/kg) was administered to animals. Blood samples were collected thereafter at different time intervals up to 24 hours.

Blood samples were collected thereafter at 0.0, 0.5, 1.0, 2.0, 4.0, 8.0, 12.0, 18.0 and 24.0 hours and analyzed for glucose levels by using GOD/POD method which was expressed as mg/100ml of blood. Then the hypoglycemic activity of pioglitazone at time‘t’ was calculated and the % of blood glucose reduction at various time intervals were calculated before and after ketoconazole treatment.

$$\% \text{ Blood glucose reduction at time 't'} = \frac{A-B}{A} \times 100$$

Where, A = Initial blood glucose level before drug administration.
B = Blood glucose levels at time‘t’ after the drug administration.

3. Results

3.1 Effect of ketoconazole *per se* treatment on blood glucose levels in healthy albino rats:

Treatment of ketoconazole (3.6 mg/kg; twice daily) has no significant influence on the blood glucose levels in normal albino rats. This indicates that ketoconazole do not possess any hypoglycemic effect. The results are compiled in figure No. 1.

3.2 Influence of ketoconazole pre-treatment on pioglitazone induced hypoglycemia in healthy albino rats

Ketoconazole pre-treatment (3.6 mg/kg; twice daily) for 7 consecutive days with pioglitazone has significantly reduced the onset of hypoglycemia (0.5-1 hr before treatment and <0.5 hr after treatment). Ketoconazole pretreatment with pioglitazone significantly enhanced peak hypoglycemia (46.57 ± 2.55 % before treatment and 63.40 ± 2.06 % after treatment). The results of these findings are graphically depicted in figure No. 2

3.3 Effect of ketoconazole *per se* treatment on blood glucose levels in healthy albino rabbits

Treatment with ketoconazole (14 mg/kg; twice a day) did not significantly alter the blood glucose level in normal albino rabbits. These finding are clearly indicating that ketoconazole do not possesses hypoglycaemic effect in healthy albino rabbits. The results are graphically depicted in figure No. 3

3.4 Influence of ketoconazole pre-treatment on pioglitazone induced hypoglycemia on healthy albino rabbits

Pre-treatment with ketoconazole (14 mg/kg; twice a day) has reduced the onset of hypoglycaemia and significantly enhanced the peak hypoglycaemia (i.e. from 41.15 % reduction to 63.23% reduction) induced by pioglitazone (1.05 mg/kg). The results of these findings is graphically depicted in figures No. 4

3.5 Influence of ketoconazole pre-treatment on pioglitazone induced hypoglycemia on diabetic albino rats:

In diabetic rats, ketoconazole (3.6 mg/kg; twice a day) pre-treatment for seven consecutive days with pioglitazone has not altered the onset of hypoglycaemia, but significantly enhanced the peak hypoglycaemia i.e. 37.48 % reduction before treatment and 46.07 % reduction after treatment. The results of these findings graphically depicted in figures No. 5.

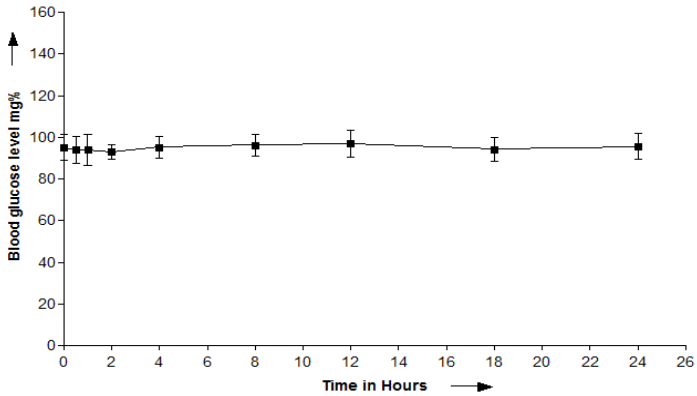

Fig No 01: Effect of ketoconazole *per se* treatment on blood glucose levels in healthy albino rats

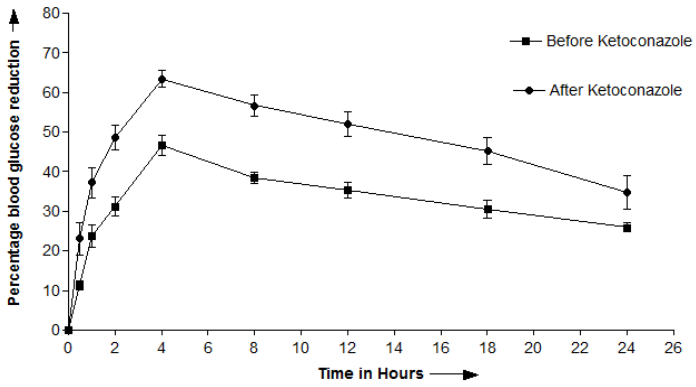

Fig NO 02: Influence of ketoconazole pre-treatment on pioglitazone induced hypoglycemia in healthy albino rats

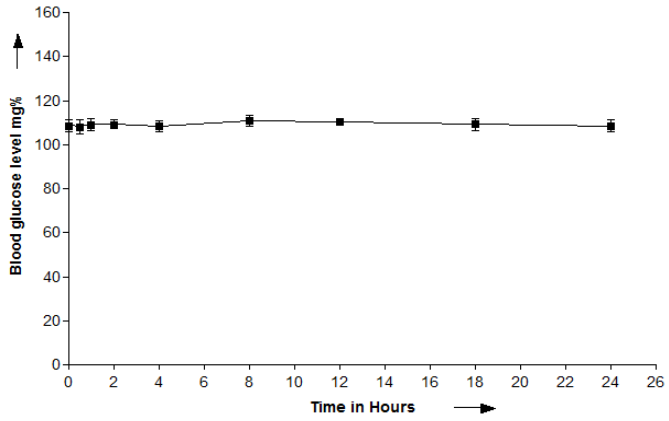

Fig No 03: Effect of ketoconazole *per se* treatment on blood glucose levels in healthy albino rabbits

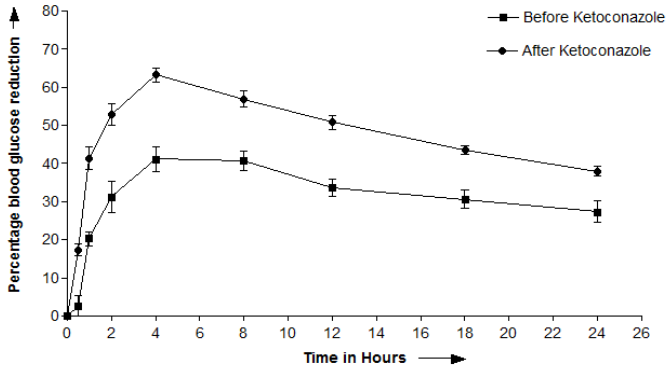

Fig No 04: Influence of ketoconazole pre-treatment on pioglitazone induced hypoglycemia on healthy albino rabbits

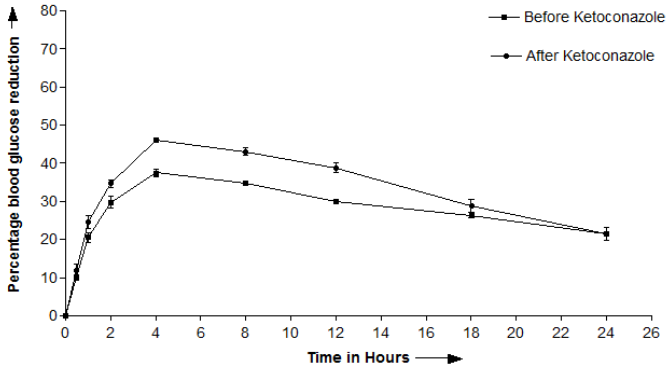

Fig. No 05: Influence of ketoconazole pre-treatment on pioglitazone induced hypoglycemia on diabetic albino rats:

4. Discussion

In changing scenario the drug molecules need to be co-prescribed with other category drugs, in which the safety aspect of the combination will be perplexing. Since, it may lead to loss of therapeutic activity / hazardous drug interactions and death of the subjects. The later is particularly true, if one of the co-administered drugs is having narrow therapeutic index. Individuals with diabetes mellitus are immunocompromised and have a greater susceptibility to a number of opportunistic fungal infections[4]. In this situation commonly use antifungal drug like ketoconazole often prescribed with oral hypoglycemic agents

like pioglitazone. However, there are plenty of reports indicating that, several co-administered drugs potentiate the hypoglycaemic activity of pioglitazone leading to adverse effects[21]. The present study was under taken to verify the possible drug-drug interaction if any between pre-treatment of ketoconazole on hypoglycemic and antidiabetic activity of pioglitazone in normal healthy rats/rabbits and diabetic rats.

Our results indicated that ketoconazole has influenced on hypoglycemic activity of pioglita-zone. In healthy rats and rabbits, pretreatment with ketoconazole enanced peak hypoglycaemic effect of poglitazone from 46.57 % to 63.40 % and from 41.15 % to 63.23 % respectively at the 4th hour which is both statistically highly significant ($p<0.01$). The onset of action reduced from 2 hours to half an hour in case of rats and 1 hour for rabbits. Most of the animals exhibited prognostic signs of hypoglycaemia, characterized by lack of interest in the surroundings and reduced physical activity. To confirm the results of the earlier study and to understand the drug-drug interaction between ketoconazole and oral anti diabetic agents in pathophysiological conditions like diabetic states, the diabetic rats were used in the latter phase of the study. In case of diabetic rats ketoconazole pretreatment with pioglitazone preponed the onset of hypoglycaemic action and there was enhancement of peak hypoglycemic activity from 37.48 % to 46.07 % at the 4th hour which is clinically and statistically significant ($p<0.001$). However, the duration of action was terminated around 24th hour. Indeed some of the animals in pioglitazone treated group exhibited hypoglycemic convulsions and rest exhibited the prognostic signs of hypoglycemia indicating the occurrence of drug-drug interaction. The possibility of additive type of drug interactions between the study drugs is ruled out; since, ketoconazole by itself is devoid of any hypoglycemic activity. Hence the ultimate possibility of drug interaction is pharmacokinetic type. As peak hypoglycemic activity of pioglitazone is enhanced significantly after ketoconazole pretreatment in every case it is inferred that, the interaction at the metabolic phase has played significant role. Oral antidiabetic drug pioglitazone is metabolised by microsomal isoenzymes CYP2C8, CYP3A4 and to lesser extent by CYP2C9[23, 24, 25]. Documented reports reveal that, the study drug ketoconazole is an inhibitor of CYP enzymes particularly 3A4, 1A2, 2C9 and 2C8[22].

Conclusion

Hence at this juncture it is concluded that the severe hypoglycemia and prolongation of hypoglycemic instances observed with pioglitazone after ketoconazole pretreatment is due to metabolic inhibition of pioglitazone by the ketoconazole. However as quoted earlier, the concentration dependent adverse incidences of pioglitazone such as pulmonary oedema, congestive cardiac failure and deaths were not occurred. It is necessary to readjust the dose/frequency of administration of oral antidiabetic drug accordingly when needs to be co-administered with ketoconazole. Further, long term studies recruiting diabetic subjects may yield quite rewarding results in this regard.

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