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Suresh Janadri *
Department of Pharmacology, Mallige College of Pharmacy, Bangalore-560090, (Karnataka), India
Email: sureshjanadri@gmail.com

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Effect of Itraconazole on Therapeutic Efficacy of Rosiglitazone in Healthy Albino Rats

Suresh Janadri*[1], Prashant Baganal [2], Rajendra Sandur [3], Ramachandra Setty [4]
[1] Department of Pharmacology, Mallige College of Pharmacy, Bangalore-560090, (Karnataka), India.
[2] Drug Testing Laboratory, Hubli-580020, (Karnataka), India.
[3] Department of Pharmacy, GRD (PG) IMT, Dehradun-248001, (Uttarakhand), India.
[4] Department of Pharmacology, Government College of Pharmacy, Bangalore-560027, (Karnataka), India.

Abstract
The most of drug-drug interaction between oral hypoglycemic agents and antifungal agents was reported in healthy rats, rabbits and diabetic rats. The aim of this study was evaluated the effect of itraconazole on therapeutic efficacy of rosiglitazone in healthy albino rats. The blood was withdrawn from the retro-orbital plexuses of rats at different time intervals at 0hr, 1, 2, 4, 8, 12, 18 and 24 hour and blood glucose was estimated by GOD-POD enzymatic method and values are expressed in mg/dl. The results indicate itraconazole enhances the onset, peak effect and duration action of rosiglitazone in healthy rats during concomitant administration of these drugs. In conclusion, the dose and frequency of administration of itraconazole and rosiglitazone should be readjusted while giving simultaneously.

Keywords: Itraconazole, Rosiglitazone, GOD-POD method.

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INTRODUCTION

The possibility of drug interactions increases as the number of drugs being taken increases or multiple drug therapy. Therefore, patients who take several drugs are at the greatest risk for interactions. The concept of drug interaction is also extended to include; drug-drug interaction, drug-food interaction, drug-herbal interaction, drug-laboratory test interaction and drug-condition interaction[1]. Drug interaction occurs when the effects of one drug are altered by another drug, food, drink or exposure to an environmental chemical[2]. Drug interaction many times leads to adverse events. These events affect millions of patients each year and are responsible for up to 5% of hospital admission[3].

Type-II diabetes mellitus is a common progressive disease affecting 1–4% of the population that leads to significantly increased comorbidity[4]. In addition to antidiabetic drugs, many other drugs may be prescribed to treat comorbidities in diabetic patients, which may result in drug interactions. It has been reported that systemic antifungal agents have been used in 3.0% of patients with Type II diabetes mellitus [4]. Rosiglitazone is one of the drug choice for the treatment of type-II diabetes. It is metabolized predominantly by the cytochrome P450, 2C8 and to a lesser extent 2C9 in the liver [5]. Whereas itraconazole is antifungal drugs inhibits mainly the CYP450 system and isoenzymes [6-7]. Hence the pharmacokinetics of drugs, that are metabolised by this enzyme system are normally affected by the simultaneously administration of itraconazole.

There are reports that itraconazole increases plasma concentration, area under the curve and elimination half-life of oral quinidine [8] and atorvastatin [9]. Itraconazole increases the plasma concentration and effects of felodipine when it was used 200mg /day for four days [10]. Itraconazole pretreatment significantly enhance the onset, peak of hypoglycemia and duration of hypoglycemic activity of pioglitazone in rats [11]. Similarly pretreatment with itraconazole also significantly altered the onset of hypoglycemic effect of thiazolidinediones, enhanced the peak hypoglycemic effect and duration of hypoglycemic effect with pioglitazone and rosiglitazone in healthy rabbits[12]. Itraconazole is one such relatively new antifungal agent and its interaction with rosiglitazone in healthy albino rats is not reported. Hence, the present study is planned to understand possible interaction between rosiglitazone and itraconazole in healthy rats.

MATERIALS AND METHODS

Animals

Adult albino rats of either sex (150-200 g) were obtained from Sri Venkateshwara Enterprises, Bangalore. India, maintained under standard in-house conditions and they were given a standard pellet diet and water *ad libitum*. All experiments carried out in accordance with the guidelines laid down by the Institutional Animal Ethical Committee (reg. no: 157/99/CPCSEA) and blood sampling was performed under ether anesthesia with taking suitable care.

Drugs

Rosiglitazone (720 µg/kg, p.o.), Itraconazole (9 mg/kg, p.o and 18 mg/kg, p.o) suspensions were prepared using 2% w/v gum acacia as suspending agent.

Method

The animals were randomly distributed in three groups consist of 6 rats per group. The Group I treated with suspension of itraconazole (18 mg/kg, p.o). Group II and group III treated with rosiglitazone (720µg/kg) per oral respectively. Blood samples were collected at 0.0, 1.0, 2.0, 4.0, 8.0, 12.0, 18.0 and 24.0 hours after treatment by retro orbital plexus and blood glucose levels were estimated by GOD/POD method. Blood glucose levels were expressed as mg/dl of blood.

In the next phase of this experiment, animals in the group II received suspension of itraconazole (9 mg/kg) per day orally for one week. Group III also received itraconazole (18 mg/kg) per day orally for one week. On the 7th day, 6 hours after administration of itraconazole the rats were fasted for 18 hours. On the 8th day, itraconazole (9 mg/kg) and Itraconazole (18 mg/kg) was administered orally to groups II and III respectively. After 60 minutes, rosiglitazone (720 µg/kg, p.o) was administered to group II and group III. Blood samples were collected there after at different time intervals for 24 hours. Blood glucose levels were estimated by GOD/POD method and expressed as mg/dl of blood.

Then the hypoglycemic activity of rosiglitazone at time‘t’ was calculated and the % of blood glucose reduction at different time intervals were calculated before and after itraconazole 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 level at time‘t’ after the drug administration

Statistical data

The data were analyzed by Student‘t’test. P values lower than 0.05 were considered as statistically significant.

RESULTS

The results are revealed that treatment with itraconazole (18 mg/kg, p.o) alone did not alter the

blood glucose levels in healthy rats (Fig No.1). However, low dose of itraconazole (9 mg/kg, p.o) pretreatment has altered the onset of hypoglycemic effect of rosiglitazone from 23.01 ± 2.17 % to 22.73 ± 1.42 % and enhanced peak hypoglycemic effect from 34.98 ± 1.64 % to 37.24 ± 1.29 % at 8th hr and duration of hypoglycemic effect was raised for more than 18 hrs. Whereas pretreatment with higher dose of itraconazole (18 mg/kg, p.o) has altered the onset of hypoglycemic effect of rosiglitazone from 23.57 ± 2.06 % to 25.97 ± 1.81 % at 2nd hour and highly significant enhanced peak hypoglycemic effect from 36.64 ± 2.64 % to 47.71 ± 1.79 % at 8th hr. Duration of hypoglycemic effect was raised for more than 24hrs (Table No.1).

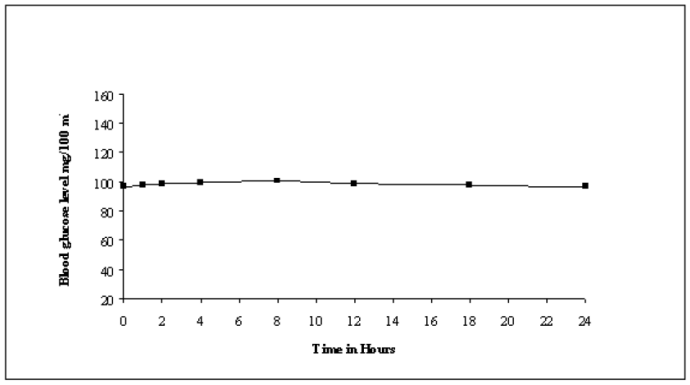

Figure 1: Effect of itraconazole (18 mg/kg. p.o) on blood glucose levels in healthy albino rats

Percentage reduction in blood glucose concentration (mean ± SEM)

Time in hr	Rosiglitazone (720µg/kg, p.o.)	Itraconazole (9mg/kg, p.o,7days) + Rosiglitazone (720 µg/kg, p.o.)	Rosiglitazone (720 µg/kg, p.o.)	Itraconazole (18mg/kg, p.o,7days) + Rosiglitazone (720 µg/kg, p.o.)
Fasting	-	-	-	-
1.0	10.44 ± 0.49	9.77 ± 0.85	13.35 ± 1.70	15.08 ± 2.06
2.0	23.01 ± 2.17	22.73 ± 1.42	23.57 ± 2.06	25.97 ± 1.81
4.0	26.17 ± 1.96	27.71 ± 0.76	27.82 ± 2.18	36.45 ± 1.27*
8.0	34.98 ± 1.64	37.24 ± 1.29	36.64 ± 2.64	47.71 ± 1.79***
12.0	23.86 ± 1.49	25.90 ± 1.14	26.25 ± 1.67	42.29 ± 0.66***
18.0	18.61 ± 1.75	22.58 ± 1.39	21.38 ± 2.16	37.76 ± 1.68***
24.0	14.56 ± 1.42	18.16 ± 1.37	16.55 ± 1.04	30.55 ± 1.68***

Table 1: Percentage decrease in blood glucose levels at different time intervals

Values are expressed in Mean±SEM, n=6 * Significant at p< 0.05; *** very highly significant at p<0.01

DISCUSSION

Patients with type II diabetes frequently have to be treated with more than one drug. Effects of oral antidiabetic drugs depend on the extent of drug absorption from the gut lumen, on metabolism of the drug in the liver, and on the extent of its excretion into bile and urine[13]. In general, modification of all these processes by a second, concomitantly administered drug can alter the effects of oral antidiabetic drugs[13].

Rosiglitazone is a novel insulin-sensitizing, oral antidiabetic agent of the thiazolidinedione for treatment of Type II diabetes mellitus, and is an effective and well-tolerated agent for lowering blood glucose[14-15]. It improves insulin sensitivity through the activation of the nuclear receptors, peroxisome proliferator-activating receptor gamma (PPAR γ)[16]. It is rapidly and completely absorbed, with absolute bioavailability estimated to be over 99% following oral administration[17]. It is metabolized through N - demethylation and p-hydroxylation, mainly by CYP2C8 and to a lesser extent CYP2C9, and does not undergo enterohepatic recirculation[18,19].

In the present study effect of itraconazole on hypoglycemic activity of rosiglitazone in healthy rats are studied. Pretreatment with itraconazole (9 and 18mg/kg, p.o) altered the onset of action, peak effect and duration of hypoglycemic effect. However, itraconazole at higher dose (18 mg/kg, p.o) significantly increased peak effect and duration of hypoglycemic action in healthy rats. It occurs due to itraconazole inhibit the cytochrome P 450 enzyme system and isoenzyme [6-7], these enzymes are responsible for metabolize the rosiglitazone. For the support of present study, clinical trial is to establish to prove the drug interaction occurs between itraconazole and rosiglitazone in healthy volunteers and diabetic patients.

CONCLUSION

Study clearly indicates that itraconazole has significantly increased the therapeutic effect of rosiglitazone in healthy rats possibly inhibiting the CYP450 enzyme system. While administered the itraconazole and rosiglitazone continuously precaution should therefore be taken to avoid the severe hypoglycemic effects. Therefore, therapeutic drug monitoring is required to readjust the therapeutic dose of these concomitantly administered drugs.

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