EFFECT OF ITRACONAZOLE ON HYPOGLYCEMIC ACTIVITY OF THIAZOLIDINEDIONE IN HEALTHY RABBITS

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Summary

Present study was conducted to evaluate the influence of itraconazole pretreatment on the hypoglycaemic effect of thiazolidinedione (pioglitazone and rosiglitazone) in healthy rabbits. Blood samples were withdrawn from marginal ear vein of rabbit at time interval for 24hrs and blood glucose was estimated by GOD/ POD method. Itraconazole (18mg/kg, p.o) pretreatment significantly altered the onset of hypoglycemic effect of pioglitazone from 16.01% to 26.04% and significantly enhanced the peak hypoglycemic effect from 27.12% to 36.21%. Similarly pretreatment with itraconazole (18mg/kg, p.o) also significantly altered the onset of hypoglycemic effect of rosiglitazone from 15.06% to 18.34% and enhanced the peak hypoglycemic effect from 18.03% to 29.26%. Duration of hypoglycemic effect raised from more than 24hrs and 18hs with pioglitazone and rosiglitazone respectively. This study indicates that therapeutic drug monitoring is required to adjust therapeutic dose of itraconazole and thiazolidinedione when used simultaneously.

Key words: Itraconazole, pioglitazone, rosiglitazone, hypoglycemic effect.

Introduction

Diabetes mellitus - a metabolic disorder characterized by abnormally elevated levels of glucose in blood and urine. More than 90% of the cases of diabetes worldwide are classified as Type-II diabetes is complex etiology and is associated with multiple defects, including impaired insulin secretion from pancreatic ß-cells and insulin resistance in peripheral tissues, primarily skeletal muscle.[1]

Sulfonylurea, thiazolidinedione and biguanides are the drug of choice in the treatment of NIDDM. Diabetics are known to develop multiple pathophysiological conditions such as nephropathy[2], retinopathy[3], cardiovascular disorders[4] and more susceptible to bacterial and other fungal infection.[5, 6] In such cases where diabetes associated with fungal infections, antifungal agents like ketoconazole, itraconazole, fluconazole, miconazole are given along with thiazolidinedione as antidiabetic drugs like pioglitazone or rosiglitazone concomitantly.

There are reports that antifungal agent like ketoconazole potentiate the hypoglycemia produced by tolbutamide in rabbits[7, 8] and humans[9]. Similarly, fluconazole interacts with sulfonylureas and potentiate their hypoglycemic effect.[10] There are also reports that itraconazole inhibit Cytochrome P-450 enzyme system[11] hence there is a possibility of pharmacokinetic type of drug interactions with concomitantly used drug(s). Pioglitazone or Rosiglitazone are metabolized by Cytochrome P-450 enzyme system.[12] Therefore the present study was conducted on healthy rabbits to assess the effect of itraconazole pretreatment on the hypoglycemic effects of pioglitazone and rosiglitazone.

Material and methods

Animals

Albino rabbits of either sex weighing 1.5-2.5kg (procured from Venkateshwara Enterprises, Bangalore) were marked for making groups and kept

in stainless steel metallic cages at ambient temperature of $28^0 \pm 2^0$ C, 45 to 55% relative humidity with 12hrs light/dark cycle. Animals were fasted for 18hrs before commencing the experiment and allowed to water *ad libitum*. Approval by IAEC (reg. no: 157/99/CPCSEA) was obtained for experimentation in the PG Department of Pharmacology, S.C.S.College of Pharmacy, Harapanahalli, India.

Drugs

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.

Study design

Rabbits in group I received suspension of itraconazole (18mg/kg, p.o), group II received pioglitazone (10mg/kg, p.o) and group III received rosiglitazone (720µg/kg p.o). Blood samples were collected at 0.0, 1.0, 2.0, 4.0, 8.0, 12.0, 18.0 and 24.0hrs after treatment through marginal ear vein and blood glucose levels were estimated by GOD/POD method expressed as mg/dl of blood.[13]

In the next phase of this experiment, animals in the group II and group III received suspension of itraconazole (18mg/kg) per day orally for one week. On the 7^{th} day, 6 hrs after administration of itraconazole the rabbits were fasted for 18 hrs. On the 8^{th} day, itraconazole (18 mg/kg) was administered orally to group II and III respectively. After 60 min, pioglitazone (10mg/kg) was administered to group II and rosiglitazone (720µg/kg) was administered to group III. Blood samples were collected at time intervals for 24 hrs and blood glucose levels were estimated. Then the hypoglycaemic activity of pioglitazone and rosiglitazone at time‘t’ was calculated and the percentage of blood glucose reduction at time intervals was calculated before and after itraconazole treatment.

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

Statistical analysis

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

Results

The data revealed that treatment with itraconazole alone did not alter the blood glucose levels in healthy rabbits. However, itraconazole pretreatment (18 mg/kg, p.o.) significantly altered the onset of hypoglycemic effect of pioglitazone from 16.01 ± 0.90 % to 26.04 ± 1.27 % and significantly enhanced peak hypoglycemic effect from 27.12 ± 1.08 % to 36.21 ± 0.60 % at 8th hr and duration of hypoglycemic effect was raised for more than 24hrs. Similarly pretreatment with itraconazole (18 mg/kg, p.o.) also significantly altered the onset of hypoglycemic effect of rosiglitazone from 15.06 ± 0.27 % to 18.34 ± 1.34 % and enhanced peak hypoglycemic effect from 18.03 ± 0.88 % to 29.26 ± 2.78 % at 8th hr. Duration of hypoglycemic effect was also raised for more than 18hrs (Table 1).

Discussion

For the assessment of the potentiation of hypoglycemic effect, onset of action (time taken to reduce minimum of 15% reduction in blood glucose levels), peak effect and duration of hypoglycemic effect (duration in which minimum of 15% reduction in blood glucose levels are maintained) were considered.

Since itraconazole (18 mg/kg, p.o) alone did not influence the blood glucose levels and thus the possibility of pharmacokinetic interaction is thereby ruled out. In our study, pretreatment with itraconazole (18 mg/kg, p.o) altered the onset of action of thiazolidinediones, where onset of action, peak effect and duration of hypoglycemic 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.[14-17] Reports also indicate that itraconazole is

a weak inhibitor of CYP1A2, CYP3A4, CYP2C9, CYP2C19 and CYP2D6.[17] It is evident from the results that the therapeutic dose of itraconazole enhanced the hypoglycemic effect of both the pioglitazone and rosiglitazone. This may be due to weak inhibitory effect of itraconazole on CYP2C9 and CYP3A4.[18] Further studies are needed to establish the effect of itraconazole pretreatment on the pharmacokinetic parameters of thiazolidinediones in humans.

Table 1: Blood glucose profile in rabbits following concomitant administration of drugs

Percentage reduction in blood glucose concentration (Mean ± SEM)					
Time in hr	**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	-0.28 ± 1.18	9.54 ± 0.40	12.16 ± 1.24	3.94 ± 0.32	5.20 ± 1.22
2.0	-1.19 ± 2.20	16.01 ± 0.90	26.04 ± 1.27**	9.50 ± 1.31	10.46 ± 0.11
4.0	-1.86 ± 1.78	25.77 ± 1.10	32.04 ± 1.67**	15.06 ± 0.27	18.34 ± 1.34*
8.0	-1.64 ± 1.43	27.12 ± 1.08	36.21 ± 0.60**	18.03 ± 0.88	29.26 ± 2.78***
12.0	-2.42 ± 2.31	18.20 ± 1.66	33.27 ± 1.39***	20.19 ± 0.66	25.11 ± 0.90**
18.0	-0.44 ± 2.08	16.26 ± 1.78	30.17 ± 1.76***	10.86 ± 0.34	18.18 ± 1.67***
24.0	-0.08 ± 1.33	9.06 ± 1.47	25.10 ± 1.06***	4.5 ± 1.12	12.58 ± 1.79***

Significant at $p < 0.05$; ** highly significant at $p<0.01$; *** very highly significant

Conclusion

The present study indicates that during the concomitant administration of thiazolidinediones such as pioglitazone and rosiglitazone as antidiabetic agents and itraconazole as antifungal agent at therapeutic doses, the dose and frequency of administration of thiazolidinediones need to be adjusted. Simultaneously blood glucose levels be regularly monitored during treatment period as precautionary measure so as to avoid severe hypoglycaemia.

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