Acta Pharmaceutica Turcica
45:37-40 (2003)

Influence of Itraconazole on Hypoglycaemic Activity of Oral Antidiabetic Agents in Healthy Albino Rabbits

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Abstract

The influence of itraconazole pretreatment for seven days on the hypoglycaemic effect of tolbutamide (40mg/kg orally) and glibenclamide (40 g/kg orally) was studied. This study was conducted on healthy albino rabbits of either sex, randomly distributed into control and test groups. The animals were fasted for 18 hours before commencement of experiment and animals were not given food throughout the period of experiment. During this period water was given ad libitum. The test groups were pretreated with itraconazole in 5% acacia suspension (30mg/kg/day for seven days). Control group received plain 5% acacia suspension. On eighth day tolbutamide and glibenclamide were administered to respective groups one hour after itraconazole. Blood samples were collected from the marginal ear veins at time intervals of 0, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 42 and 48 hours and glucose levels were estimated by using GOD/POD method.

The study indicated that itraconazole pretreatment has enhanced the hypoglycaemic effect of tolbutamide significantly, whereas that of glibenclamide's was not influenced significantly. The study suggested that the dose and/or frequency of tolbutamide administration has to be readjusted accordingly when tolbutamide and itraconazole need to be used concomittantly.

Key words: Itraconazole, tolbutamide, glibenclamide, hypoglycaemic activity

Introduction

Diabetes mellitus is a chronic metabolic disorder characterised by elevated blood glucose levels known as hyperglycaemia, it requires careful management by drugs associated with diet control. Sulfonylureas are the drug of choice in the treatment of NIDDM. There are reports that diabetic patients develop multiple pathology such as nephropathy, retinopathy, cardiovascular disorders etc. In addition they are susceptible to bacterial (of respiratory tract) and fungal infections etc. In such conditions other specific drugs are used along with the routine sulfonylurea dose. This may cause a problem of drug-interactions.

There are reports that about 7% of the diabetic patients get fungal infections. In such patients various antifungal drugs are prescribed along with sulfonylureas for a specified period. There are reports that antifungal drugs like ketoconazole potentiate the hypoglycaemia produced by tolbutamide in rabbits (Krishnaiah *et al.*, 1993 and 1994) and humans(Krishnaiah *et al.*, 1994). Similarly, fluconazole interacts with sulfonylureas and potentiate their hypoglycaemic effect (Lazer, J.D. *et al.*, 1990). During the usage of such drugs with sulfonylureas, the dose and frequency of administration of sulfonylureas must be readjusted so as to avoid the development of severe and fatal hypoglycaemia. Itraconazole is one such relatively new antifungal agent and its interaction with sulfonylureas is not studied and established. Hence in the present study this interaction is investigated in healthy albino rabbits.

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Materials and Methods

The study was conducted on healthy albino rabbits of either sex weighing between 1.5 - 2.0 kg and were procured from the central animal house, V.L. College of Pharmacy. The animals were randomly distributed into different groups. The animals were kept in colony cages at ambient temperature of 28° ± 2° C and 4.5 - 5.5% relative humidity with a 12 hour light/12 hour dark cycle.

Itraconazole was obtained from M/s Glenmark Pharmaceuticals, Nasik, glibenclamide from Hoechst India Ltd., Mumbai and tolbutamide from Albert David, Mumbai.

Drug treatment: Itraconazole (30 mg/kg, p. o. for seven days), glibenclamide (40 g/kg, p.o.) and tolbutamide (40mg/kg, p. o.). All these drugs were suspended separately in 5% acacia suspension in distilled water. Plain acacia suspension was used as control.

Experimental Procedure: Healthy rabbits were suitably marked and randomly distributed into four groups. All animals were fasted for 18 hours with water ad libitum. Animals of groups 1 and 2 were administered tolbutamide (40 mg/kg, p. o.) and groups 3 and 4 received glibenclamide (40 g/kg, p. o.). Blood samples were collected from the marginal ear vein at 0, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 42, 48 hours and blood glucose levels were estimated by GOD/POD method (Trinder .P., 1964). In the next phase of the experiment the animals of groups 1 and 3 received plain acacia suspension (0.5 ml/day for seven days) and served as control and the animals of groups 2 and 4 received itraconazole 30 mg/kg/day for seven days. On the seventh day 6 hours after itraconazole administration, the animals were fasted for 18 hours and water was given ad libitum. On the eighth day itraconazole/ acacia suspension were given as usual. One hour after the treatment animals of groups 1 and 2 received tolbutamide and groups 3 and 4 received glibenclamide. 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 and graphically depicted in figure.

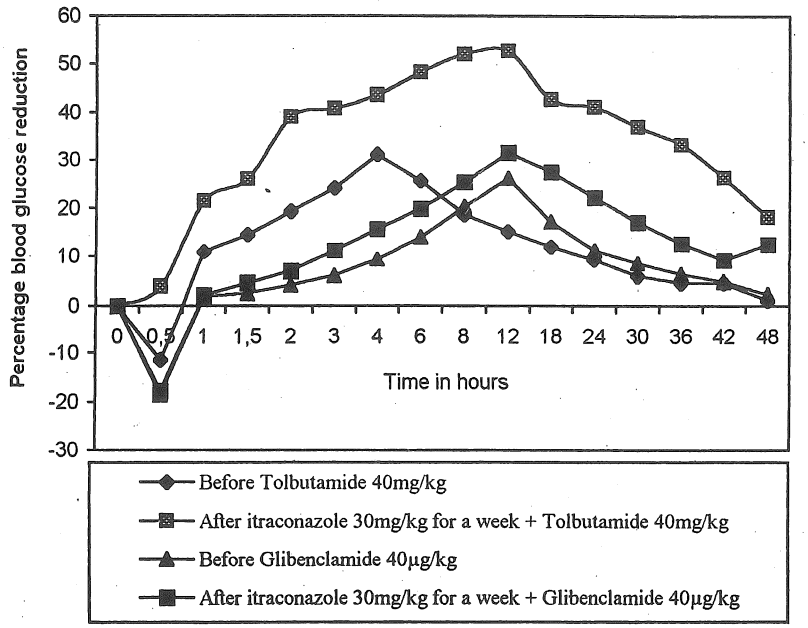
Statistical Analysis: The data were analysed by using Students' t-test. P values lower than 0.05 were considered as statistically significant.

Table 1. Effect of Itraconazole on Tolbutamide and Glibenclamide Induced Hypoglycaemia in Healthy Rabbits

Time In hrs.	% blood glucose reduction by tolbutamide before and after itraconazole treatment		% blood glucose reduction by glibenclamide before and after itraconazole treatment	
	Before	After	Before	After
Fasting	----	----	----	----
0.5	-11.42 ± 2.21	03.79 ± 7.86	-18.56 ± 3.83	-17.73 ± 7.19
1.0	10.88 ± 2.65	21.55 ± 6.34	01.87 ± 2.08	02.09 ± 3.50
1.5	14.51 ± 3.81	26.09 ± 6.25	02.48 ± 2.00	04.53 ± 3.35
2.0	19.40 ± 4.58	38.95 ± 8.46	04.08 ± 1.57	06.85 ± 3.17
3.0	24.13 ± 4.68	40.77 ± 7.78	05.97 ± 1.82	11.22 ± 3.70
4.0	31.06 ± 4.22	43.59 ± 6.70	09.31 ± 3.26	15.75 ± 3.60
6.0	25.61 ± 3.32	48.18 ± 5.88*	13.99 ± 4.20	19.93 ± 3.06
8.0	18.66 ± 2.46	51.92 ± 5.80*	20.24 ± 3.66	25.39 ± 3.12
12.0	15.23 ± 1.55	52.70 ± 8.19*	26.20 ± 4.61	31.46 ± 2.44
18.0	11.96 ± 1.33	42.58 ± 6.50*	17.17 ± 4.29	27.57 ± 3.48
24.0	09.20 ± 1.06	40.99 ± 7.12*	11.25 ± 2.08	22.22 ± 4.22
30.0	05.89 ± 1.24	36.86 ± 6.75*	08.57 ± 1.33	17.07 ± 2.62*
36.0	04.53 ± 0.71	33.18 ± 6.60*	06.24 ± 0.89	12.70 ± 2.22
42.0	04.47 ± 0.83	26.31 ±5.39*	04.79 ± 1.21	09.14 ± 2.05
48.0	01.04 ± 1.76	18.14 ± 4.28*	02.20 ± 0.88	12.48 ± 2.96

*Statistically significant $P < 0.05$

Fig. Effect of Itraconazole on Tolbutamide and Glibenclamide Induced Hypoglycaemia in Healthy Rabbits



Results and Discussion

For the assessment of the potentiation of hypoglycaemia, onset of action, (time taken to induce a minimum of 15% reduction in blood glucose levels), peak effect, duration of hypoglycaemia (duration in which minimum of 15% reduction in blood glucose levels are maintained) were considered. From the table, it is evident that after the itraconazole treatment the parameters of tolbutamide induced hypoglycaemia are altered significantly, i.e. peak effect was enhanced from 31.06% 4.22 at 4 hours to 52.70 8.19 at 12 hours and there was a prolongation of duration from about 12 hours to about 48 hours, but onset of action was reduced. In case of glibenclamide induced hypoglycaemia, itraconazole has altered the parameters insignificantly. In the control group acacia suspension for seven days has not influenced the hypoglycaemia induced by both tolbutamide and glibenclamide.

The drug interaction studies are normally conducted in animal models to find out the type and mechanism of interaction. In the present study, rabbits are used as animal model since, it is one of the animal model used for the bioassay of insulin and handling and collection of required number of blood samples is easier. In clinical practice, all drugs of this study are administered through oral route, hence, we have also administered them orally. Sulfonylureas are normally metabolized by the microsomal enzyme system (Singh *et al.*, 1980) especially cytochrome P 450 enzyme system and other enzymes to hydroxy and then to carboxy metabolites (Wester M.R. *et al.*,1999) There is a report that itraconazole can inhibit the metabolism of drugs that are metabolized by cytochrome P - 450 3A group of enzymes(Pohjola - Sintonen S *et al.*, 1993). In the present study, the duration and peak effect of tolbutamide induced hypoglycaemia is enhanced significantly. Probably this may due to the inhibitory effect of itraconazole on cytochrome p 450 enzyme systems. However further studies are in progress so as to confirm the same by directly estimating blood and urine concentrations of tolbutamide and its metabolites, before and after itraconazole treatment. However, the present study suggests that the dose and frequency of administration of tolbutamide must be readjusted when it is concomitantly used with itraconazole.

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Accepted: 21.08.2002