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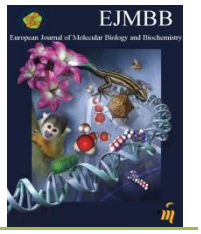

INFLUENCE OF REPEATED ADMINISTRATION OF SERTRALINE ON THE ANTIDIABETIC ACTIVITY OF PIOGLITAZONE IN DIABETIC RATS

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ABSTRACT
The present study was carried out the repeated administration of sertraline on the antidiabetic activity of pioglitazone in alloxan induced diabetic rats. The blood was withdrawn from the retro-orbital plexuses of pioglitazone treated rats at different time intervals at 0 hr, 1, 2, 4, 8, 12, 18, 24 hour before and after administration of sertraline. The blood glucose was estimated by GOD-POD enzymatic method using semi-autoanalyzer and data are expressed in mg/dl. The results indicate sertraline increases the onset, peak effect and duration action of pioglitazone in diabetic rats during simultaneous administration of these drugs. In conclusion the dose and frequency of administration of sertraline and pioglitazone should be adjusted while administrating concomitantly.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder. Its incidence differs in different countries, corresponding to 10% of the general American population [1]. Diabetes causes secondary diabetic complications leads to loss of organ function and organ failure [2]. There is a high incidence of depression in diabetic patients and risk is 15 to 20% greater than the risk for the general population [3-5]. Both these pathological conditions a patient has to take oral hypoglycemic drugs and antidepressant drugs concomitantly.

Pioglitazone - a thiazolidinedione class of drug acts by targeting insulin resistance by interacting with the gamma subtype of the peroxisome proliferator-activated receptor (PPAR) [6].

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This results in an increase in insulin sensitivity in skeletal muscle, liver, and adipose tissues [7]. The iso-enzyme CYP2C9, CYP2C8 is responsible for metabolism of pioglitazone [8] whereas sertraline produces time-dependent inhibition of CYP3A4 and/or other P450 enzymes [9]. Hence the pharmacokinetics of drugs, that are metabolised by this enzyme system are normally affected by the concomitant usage of sertraline. There are reports that patient with schizoaffective disorder with non-insulin dependent diabetes mellitus treated with sertraline, risperidone and glyburide who developed hypoglycemia [10]. Sertraline potentiated the effects of haloperidol, bisacodyl and flucloxacillin [11]. However there is a report that the patients required dextrose infusion when treated with sertraline and glibenclamide [11]. Antidepressant drugs (sertraline) added to liver microsomes of control rats inhibited the rate of 7-hydroxylation of warfarin [12]. Serotonin is selective serotonin reuptake inhibitor interaction with pioglitazone in diabetic rats is not

reported. Hence the present study is planned to possible interaction between pioglitazone and sertraline in diabetic rats.

MATERIAL AND METHODS

Experimental Animals

Wistar albino rats of either sex (150-200 g) were obtained from Sri Venkateshwara Enterprises, Bangalore. India. The animals were kept in colony cages at ambient temperature of 28º±2ºC and 45 to 55% relative humidity with a 12 hour light / dark cycle. The animals were fasted for 18 hours before commencing the experiment and they were given Amruth pellet diet and water *ad libitum*. Experiments carried out in accordance with the guidelines laid down by the IAEC (reg. no: 157/99/CPCSEA).

Method

A solution of alloxan was prepared in normal saline to represent 120 mg/ml, administered intra-peritoneal to 18 hour fasted rats for induction of diabetes. Blood glucose was estimated for these animals to confirmed attaining the pathological condition as diabetes mellitus. The diabetic animals were divided into two groups consist of 6 rats per group. The Group-I received suspension of sertraline (18 mg/kg, p.o) and Group II received with pioglitazone (10 mg/kg, p.o.) 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 experiment, animals in the group II received suspension of sertraline (18 mg/kg) per day orally for one week. On the 7th day, 6 hours after administration of sertraline the rats were fasted for 18 hours. On the 8th day, sertraline (18 mg/kg) was administered orally to groups II. After 60 minutes, pioglitazone (10 mg/kg, p.o) was administered to group II. Blood samples were collected at different time intervals for 24 hours. Blood glucose values were estimated by GOD/POD method and expressed as mg/dl of blood.

Statistical Data

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

RESULTS

Data are revealed that pretreatment with sertraline (18 mg/kg, p.o) alone did not modify the blood glucose levels in healthy rats. Pretreatment with sertraline (18 mg/kg, p.o) for 8 days continuously has significant ($p<0.05$) altered the onset of hypoglycemic effect of pioglitazone from 27.40±2.52 % to 33.57±4.43 at 2nd hour and significant ($p<0.001$) enhanced peak hypoglycemic effect from 53.05± 1.67% at 12 hour to 64.33±1.69 % at 8th hour. Duration of hypoglycemic effect was raised for more than 24 hours (Table 1).

Table 1. Percentage decrease in blood glucose levels at different time intervals before and after administration of sertraline

Time in hr	Sertraline (18 mg/kg, p.o.)	Pioglitazone (10 mg/kg, p.o.)	Sertraline (18 mg/kg, p.o, 7 days) + Pioglitazone (10 mg/kg, p.o.)
Fasting	-	-	-
1.0	-0.85	13.92 ± 0.53	12.46 ± 1.54
2.0	-0.75	27.40 ± 2.52*	33.57 ± 4.43*
4.0	0.43	46.58 ± 1.75*	56.17 ± 1.77**
8.0	-3.01	52.40 ± 1.37**	64.33 ± 1.69***
12.0	-2.20	53.05 ± 1.67**	55.94 ± 3.06**
18.0	-0.47	30.71 ± 2.97*	52.82 ± 2.94**
24.0	0.31	23.78 ± 2.70*	51.07 ± 2.93**

*Values are expressed in Mean±SEM, n=6, * p< 0.05; ** p<0.01; *** p<0.001.*

DISCUSSION

Diabetes affected with 15-20% of depression compared with general population. Both these pathological conditions, physician prescribe antidiabetic and antidepressants class of drugs for prolonged period. Such a long time administration of these drugs, there is possibility of occurrence of drug interaction at absorption, distribution, metabolism, excretion, enzymatic and receptor site. Richelson *et al*, have shown that SSRIs (Fluoxetine, Sertraline, Paroxetine and Fluvoxamine) and other newer antidepressants (Venlafaxine, Nefazodone and Mitrazapine) are potent inhibitors of CYPs of the liver. The iso forms of CYPs like CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 are inhibited and may produce drug interactions with the commonly other drugs metabolised by these isoenzymes [13]. Reported on pretreatment with sertraline (15 mg/kg and 30 mg/kg) has enhanced duration and peak hypoglycaemia induced by both tolbutamide and glibenclamide in healthy rats, rabbits and diabetic rats [14]. On this basis, present study has planned to perform drug interaction of pretreatment of sertraline with pioglitazone

in diabetic rats. There is alteration of onset, peak and duration of pioglitazone concomitantly administered with sertraline due to inhibition of CYP3A4 and/or other P450 enzymes these enzymes are also responsible for metabolism of pioglitazone drug.

CONCLUSION

The study indicates sertraline enhances onset, peak hypoglycemia and duration of action of pioglitazone in diabetic rats therefore therapeutic drug monitoring is required to readjust the dose of these concurrently administered drugs.

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