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Research Article

PHARMACOKINETIC CHANGES OF FLUVOXAMINE AND PIOGLITAZONE BY DRUG DRUG INTERACTION IN HEALTHY, DIABETIC AND DEPRESSIVE RATS

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ABSTRACT

Objective: The present work studied the pharmacokinetic drug interactions between fluvoxamine and pioglitazone in healthy and disease rats following single and multiple dosage treatment.

Materials and Methods: The study was conducted on Streptozotocin (STZ) induced type 2 diabetic rats and despair swim test induced depressive rats. Single day (SD) and multiple days (MD) pharmacokinetic of fluvoxamine (Flu), pioglitazone (Pio) alone and their combinations were performed in healthy, diabetic and depressive rats. Pharmacokinetic parameters were analyzed.

Results: Pioglitazone and fluvoxamine has shown increase in their concentrations in both healthy and diseased rats compared to given alone. Single day administration of combination has shown significant increase in concentration of pioglitazone, while there was no significant change in concentration of fluvoxamine in both healthy and diseased animals. Multiple days administration of pioglitazone has shown no influence on pharmacokinetics of fluvoxamine in both healthy and depressive animals. However, fluvoxamine has shown significant improvement in pharmacokinetic profile of pioglitazone, when administered in combination for multiple days in healthy and diabetic rats. This may be due to inhibition of CYP (cytochrome P-450) enzyme by fluvoxamine, the enzyme through which pioglitazone gets metabolized.

Conclusion: In the present study, fluvoxamine has shown significant influence on pharmacokinetics of pioglitazone, which indicates a pharmacokinetic type of interaction between fluvoxamine and pioglitazone has occurred.

Keywords: Type 2 Diabetes mellitus, Depression, Fluvoxamine, Pioglitazone, Streptozotocin.

INTRODUCTION

Drug–drug interactions may occur when more than one drug is administered in a patient to treat a single ailment or multiple ailments. The concomitant use of several drugs is often desired to obtain a therapeutic objective or to treat co-existing diseases. Simultaneous use of several drugs may lead to drug–drug interactions. The net result of interaction may be enhanced or diminished effects of one or both the drugs or the appearance of a new effect that is not seen with either drug alone [1]. There are several diseases those require lifelong treatment such as diabetes and hypertension. Patients with such diseases will often need to be administered drugs for treatment of other co-existing diseases, either for a short period or lifelong [2]. In the present study, two diseases (diabetes and depression) those may co-exist and require chronic treatment with the possibilities of occurrences of interactions between the concurrently used drugs.

Diabetes is a chronic metabolic disorder characterized by hyperglycemia caused by insufficient insulin, often combined with insulin resistance requires lifelong treatment. Diabetic patients may also be affected with many other diseases like depression, peptic ulcer, hypertension and fungal infections, which require prolong treatment [3]. Depression is another such disorder that requires chronic treatment. There are several candidates who suffer from both diabetes and depression. There are reports that only 50% of patients with depression and diabetes receive adequate antidepressant treatment and fewer than 50% complete four or more visits for psychotherapy. Since both the disorders require prolonged medication, there is every chance of a drug-drug interaction.

There are reports indicating many antidepressants, especially selective serotonin reuptake inhibitors produce effect on insulin and reduce glucose levels [4]. Pioglitazone, an insulin sensitizer prolongs the antidepressant activity of sertraline. Fluvoxamine increases the peak effect of glibenclamide [5]. However, there is no such report regarding interactions between fluvoxamine and pioglitazone. Hence, the present study planned to assess the interaction between fluvoxamine and pioglitazone.

MATERIALS AND METHODS

Animals

Male wistar rats aged 8-9 weeks (200–250g) were selected for the study. The animals were caged individually in an animal room with 12-hour (hr) dark/light cycles at ambient temperature of 25±2°c. The experimental protocol was approved by the Animal Ethical Committee. The animals were handled in accordance with the Institutional Guidelines for the Care and Use of Animals for Experimental Purposes. The rats were provided standard food and water *ad libitum.*

Drugs

Pioglitazone was gift sample from micro labs, Bangalore and fluvoxamine was obtained from SIGMA (St. Louis, MO, USA). All other chemicals used were of analytical grade.

Experimental procedures

Streptozotacin (STZ) induced diabetes

At neonatal stage, STZ was administered at day 2 and day 3 of birth at a dose of 45 mg/kg in citrate buffer at pH 4.5, which result in diabetic condition. At the end of 8th week of their age, oral glucose tolerance test was done at a dose of 3 gm/kg of glucose to evaluate the diabetic condition in rats. The rats which have 45% high glucose AUC (area under curve) compared to normal control were selected for the study [6].

Chronic forced swim stress induced depression

The rats were individually forced to swim for 6 minutes in plastic cylinders (height 37 cm, diameter 15.5 cm) for 14 days, which contained water to a height of 20 cm. The total period of immobility during the 6 minutes testing period was recorded. Rats which are consistent in high immobility time were selected for the study [7].

Pharmacokinetic study

The normal, diabetic and depressive rats were marked conveniently and distributed randomly into groups of 6 animals each separately.

Pioglitazone was administered at a dose of 5 mg/kg and fluvoxamine at a dose of 50 mg/kg, orally to their respective groups [8].

Pharmacokinetic interaction study in normal rats

Group 1 was served as normal control, which received vehicle. Group 2 and 3 were served as treatment groups, which received fluvoxamine and pioglitazone respectively. Group 4 was served as treatment group (SD), which received fluvoxamine, followed by pioglitazone after 30 minutes. Group 5 was served as treatment group (SD), which received pioglitazone, followed by fluvoxamine after 30 minutes. Group 6 was served as treatment group (MD), which received fluvoxamine for 8 days, followed by pioglitazone after 30 minutes on 8th day. Group 7 was served as treatment group (MD), which received pioglitazone for 8 days, followed by fluvoxamine after 30 minutes on 8th day.

Pharmacokinetic interaction study in diabetic and depressive rats

Group 1 and 2 were served as diabetic and depressive control, which received vehicle. Group 3 rats were diabetic which received pioglitazone and group 4 rats were depressive which received fluvoxamine. Group 5 rats were diabetic (SD), which received fluvoxamine, followed by pioglitazone after 30 minutes. Group 6 rats were depressive (SD), which received pioglitazone, followed by fluvoxamine after 30 minutes. Group 7 rats were diabetic (MD), which received fluvoxamine for 8 days, followed by pioglitazone after 30 minutes on 8th day. Group 8 rats were depressive (MD), which received pioglitazone for 8 days, followed by fluvoxamine after 30 minutes on 8th day.

All the animals were over night fasted with water *ad libitum*. Animals were administered with their respective treatments. Blood was collected at 0, 0.25, 0.5, 1, 2, 4, 8 and 24th hour. Samples were centrifuged at 8000 rpm for 10 minutes, plasma was collected and subjected for high performance liquid chromatography (HPLC) analysis.

Pharmacokinetic data analysis

The maximum plasma concentration (C_{max}), time needed to reach the maximum plasma concentration (T_{max}), area under the concentration–time curve (AUC_{0-24}), mean residence time (MRT), elimination rate constant (K_{el}) and half life ($T_{1/2}$) were calculated using non compartmental pharmacokinetic model of WinNonlin-5.3 [9].

Statistical analysis

The results were expressed as mean±SEM. The significance was determined by applying one way ANOVA.

RESULTS AND DISCUSSION

With increasing co-incidence of diabetes and depression, the co-administration of antidepressant drugs with antidiabetic drugs becomes essential. Pioglitazone is a thiazolidinedione derivative antidiabetic agent that acts primarily by decreasing hepatic and peripheral insulin resistance, therefore improving hyperglycemia and hyperlipidemia in type 2 diabetes mellitus [10]. Fluvoxamine is a selective inhibitor of serotonin reuptake that is widely used in the management of depression [11]. The experiment is designed to study the effect of single and multiple dosing of pioglitazone and fluvoxamine on absorption, metabolism and elimination, hence we have estimated plasma concentration at 0.25th, 0.5th, 1st and 2nd hour to observe its effect on absorption, 4th and 8th hour to study the effect on peak effect and 24th hour on metabolism/excretion in normal, diabetic and depressive rats. The normal rat model served to quickly identify the interaction and the depressive and diabetic rat model served to validate the same response in diseased condition [12].

In the present study, pharmacokinetic parameters of pioglitazone reveals that its peak effect was at 4th hour and $T_{1/2}$ was 3.6th and 4th hour in normal and diabetic rats respectively. Pioglitazone was well absorbed after oral administration, concentration of 1.2 and 1.7 mcg/ml was observed at 1st hour and it was increased to peak at 4th hour i.e. 5.65 and 6.16 mcg/ml in both normal and diabetic rats respectively. It started declining at 8th hour and showed a negligible concentration of 0.009 mcg/ml in normal rats and 0.016 mcg/ml in diabetic rats at the end of 24th hour. These results confirm its prolonged action after single dose administration.

Fluvoxamine has shown significant increase in C_{max} of pioglitazone upon treatment for single day and multiple days in normal rats when compared with pioglitazone alone (8.54±0.46 (P<0.001), 6.91±0.50 (P<0.05) vs. 5.55±0.47). Single and multiple dosing of fluvoxamine also increased the concentration of pioglitazone in diabetic rats (8.90±0.52, 7.28±1.30 vs. 5.91±0.52) but significant only in multiple dosing (P<0.01). Peak effect was seen at 4th hour and slightly starts declining from 8th hour. Repeated administration of fluvoxamine significantly increases AUC levels which indicate significant effect of fluvoxamine on pioglitazone absorption profile in both normal (70.58±2.69 (P<0.001) vs. 42.42±4.13) and diabetic animals (96.05±6.51 (P<0.01) vs. 51.19±13.45). The effect of metabolism was also found to be significant since the fluvoxamine treatment produced improvement in $T_{1/2}$ and K_{el}. The $T_{1/2}$ of pioglitazone was significantly increased after the fluvoxamine treatment for single day and multiple days in normal rats (4.35±0.28 (P<0.05) vs. 3.62±0.22), single day and (4.86±0.25 (P<0.001) vs. 3.62±0.22), multiple days and diabetic rats (4.32±0.21 (P<0.05) vs. 3.86±0.09), single day and (4.78±0.26 (P<0.001) vs. 3.86±0.09), multiple days. It was interesting to observe here that even though both drugs were metabolized by same CYP enzyme, the above results indicate that there was significant interaction between these two drugs at metabolism site as well. It was also observed that fluvoxamine increased MRT and also delay the clearance of pioglitazone in single and 7 days treatment when compared with pioglitazone alone. This indicated the interaction occurring at excretion site as well.

Single day pharmacokinetic of fluvoxamine has shown that fluvoxamine has peak effect at 0.5th hour in both normal and depressive rats. Single day administration of pioglitazone did not influence the pharmacokinetic of fluvoxamine. Rats treated with repeated doses of pioglitazone have not shown significant changes in pharmacokinetic of fluvoxamine in both normal and depressive rats. The AUC (normal rats, 3.73±0.43, 3.82±0.45 vs. 3.79±0.33), (depressive rats, 5.52±0.86, 5.13±0.31 vs. 5.46±0.32) and $C_{max,}$ (normal rats, 1.11±0.21, 1.03±0.17 vs. 1.09±0.19), (depressive rats, 1.22±0.18, 1.19±0.19 vs. 1.24±0.18) of fluvoxamine did not change significantly upon pioglitazone treatment. The time of peak concentration remained same at 0.5th hour, even before and after pioglitazone treatment. These result confirmed that pioglitazone has no effect on fluvoxamine absorption and metabolism. It is also observed from the data in the table no. 3 and 4 that pioglitazone also failed to show the significant effect on clearance indicated that the interaction at excretion site is also ruled out in both normal and diseased rats.

Table 1: Mean pharmacokinetic parameters of pioglitazone alone and during fluvoxamine treatment in normal rats

Parameters	Pio	Pio+Flu (SD)	Pio+Flu (MD)
C_{max} (mcg/ml)	5.55±0.47	6.91±0.50 *	8.54±0.46***
T_{max} (hr)	4.00±0.00	4.00±0.00	4.00±0.00
AUC_{0-24h} (hr*mcg/mL)	42.42±4.13	57.34±6.10**	70.58±2.69***
$T_{1/2}$ (hr)	3.62±0.22	4.35±0.28*	4.86±0.25***
K_{el} (1/hr)	0.192±0.01	0.160±0.01**	0.143±0.01***
MRT (hr)	5.58±0.140	5.80±0.07	5.83±0.12*

Mean ±SEM (n=6), ***p<0.001, **p<0.01, *p<0.05 compared to pioglitazone control.

These data confirmed that single and multiple dosing of fluvoxamine increased concentration of pioglitazone but pioglitazone has shown no change in pharmacokinetics of fluvoxamine in both normal and diseased rats. Pioglitazone was mainly metabolized by CYP2C8, CYP2C9 and CYP3A4 [13,14,15] and fluvoxamine was metabolized by CYP2C19, CYP2C9 and CYP3A4 [16]. The mechanism that underlies the interaction between fluvoxamine and pioglitazone probably involves the inhibition of CYP3A4 or CYP2C9 catalysed pioglitazone metabolism by fluvoxamine. Concomitant administration of fluvoxamine could thus result in increased plasma concentrations of pioglitazone.

Table 2: Mean pharmacokinetic parameters of pioglitazone alone and during fluvoxamine treatment in diabetic rats

Parameters	Pio	Pio+Flu (SD)	Pio+Flu (MD)
C_{max} (mcg/ml)	5.91±0.52	7.28±1.30	8.90±0.52**
T_{max} (hr)	4.00±0.00	4.00±0.00	4.00±0.00
AUC $_{0\text{-}24h}$ (hr*mcg/mL)	51.19±13.5	73.16±7.67*	96.05±6.51**
$T_{1/2}$ (hr)	3.86±0.09	4.32±0.21*	4.78±0.26***
K_{el} (1/hr)	0.180±0.004	0.163±0.01**	0.146±0.01***
MRT (hr)	5.84±0.29	6.27±0.13*	6.32±0.05*

Mean ±SEM (n=6), ***p<0.001, **p<0.01, *p<0.05 compared to pioglitazone control.

Table 3: Mean pharmacokinetic parameters of fluvoxamine alone and during pioglitazone treatment in normal rats

Parameters	Flu	Flu+Pio (SD)	Flu +Pio (MD)
C_{max} (mcg/ml)	1.09±0.19	1.03±0.17	1.11±0.21
T_{max} (hr)	0.50±0.00	0.50±0.00	0.50±0.00
AUC $_{0\text{-}24h}$ (hr*mcg/mL)	3.79±0.33	3.82±0.45	3.73±0.43
$T_{1/2}$ (hr)	4.37±0.56	4.85±0.79	4.59±0.57
K_{el} (1/hr)	0.161±0.02	0.147±0.02	0.154±0.02
MRT (hr)	3.79±0.58	4.44±0.93	4.09±0.61

Mean ±SEM (n=6), ***p<0.001, **p<0.01, *p<0.05 compared to fluvoxamine control.

Table 4: Mean pharmacokinetic parameters of fluvoxamine alone and during pioglitazone treatment in depressive rats

Parameters	Flu	Flu+Pio (SD)	Flu +Pio (MD)
C_{max} (mcg/ml)	1.24±0.18	1.19±0.19	1.22±0.18
T_{max} (hr)	0.50±0.00	0.50±0.00	0.50±0.00
AUC $_{0\text{-}24h}$ (hr*mcg/mL)	5.46±0.32	5.13±0.31	5.52±0.86
$T_{1/2}$ (hr)	4.64±0.57	5.21±0.71	4.76±0.04
K_{el} (1/hr)	0.152±0.02	0.136±0.02	0.146±0.001
MRT (hr)	4.19±0.63	4.74±0.76	4.34±0.10

Mean ±SEM (n=6), ***p<0.001, **p<0.01, *p<0.05 compared to fluvoxamine control.

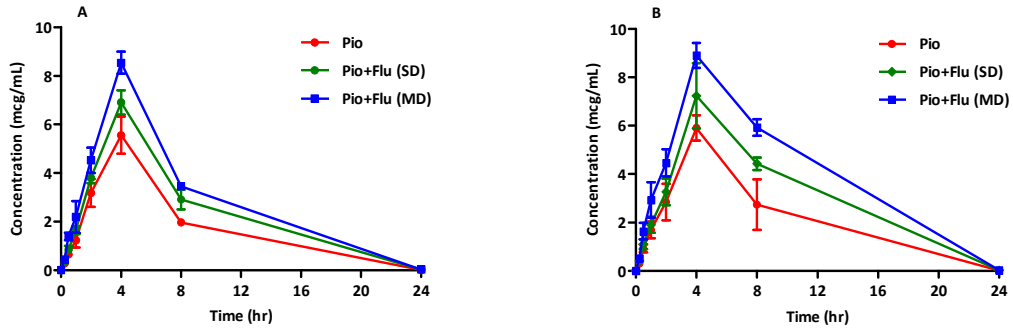
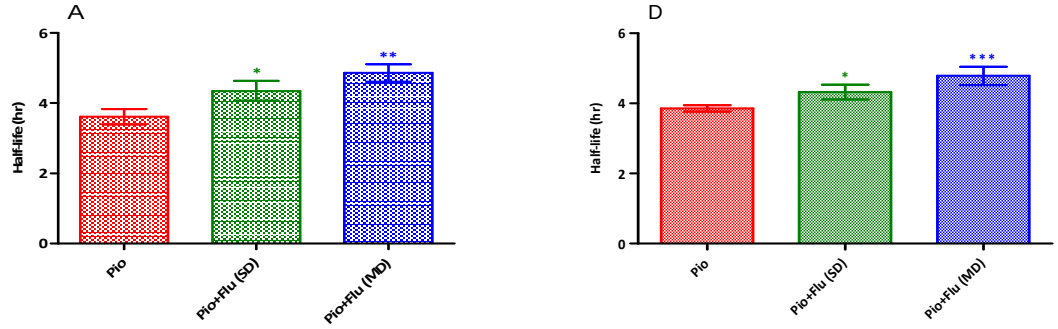


Fig. 1: Plasma concentrations time curves of pioglitazone following its oral administration at 5 mg/kg in control and fluvoxamine (50 mg/kg) pre-treated (SD & MD) normal (1A) and diabetic (1B) rats. Data are expressed as mean±SEM in (n = 6) rats.



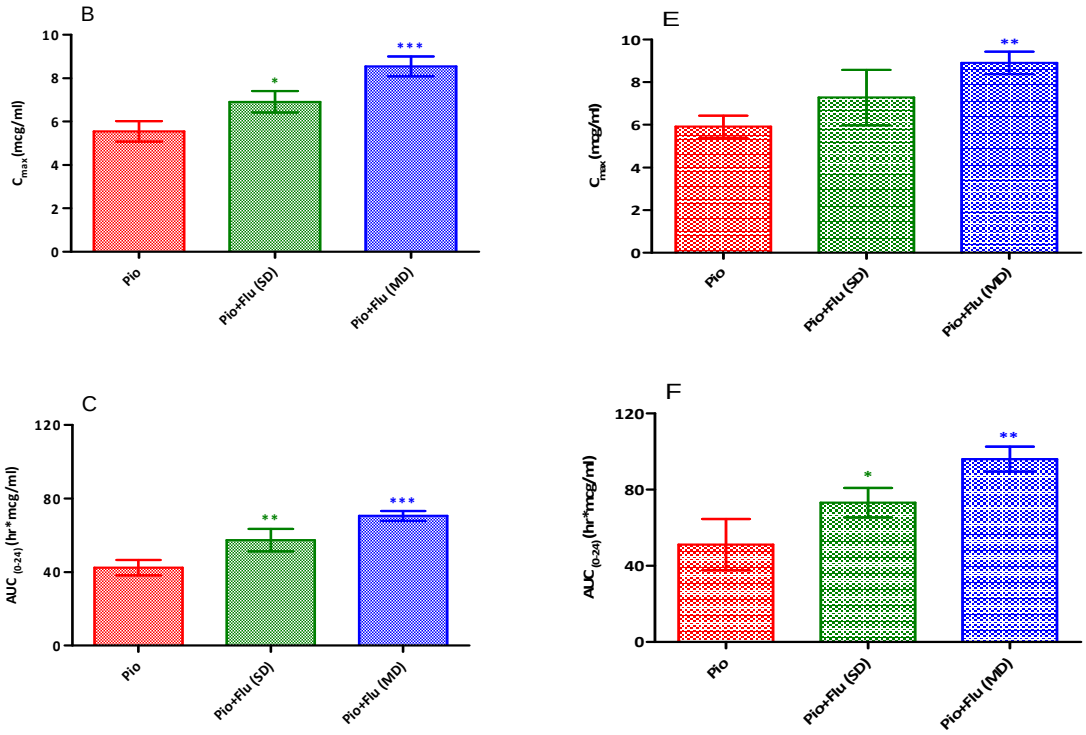


Fig. 2: A, B, C and D, E, F represent pharmacokinetic parameters in normal and diabetic rats respectively. Half life, C_{max} and AUC of pioglitazone following its oral administration at 5 mg/kg in control and fluvoxamine (50 mg/kg) pre-treated (SD & MD) normal (A, B, C) and diabetic (D, E, F) rats respectively. Data are expressed as mean±SEM in (n = 6) rats.

CONCLUSION

The interaction observed between pioglitazone and fluvoxamine appears to be pharmacokinetic interaction at absorption, metabolism and excretion levels.

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