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Influence of Olanzapine on the Pharmacodynamics and Pharmacokinetics of Pioglitazone in Animal Models

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A B S T R A C T

The present study was performed to investigate the effect of olanzapine on the pharmaco dynamics and pharmacokinetics of pioglitazone in rats (normal and diabetic) and rabbits to evaluate the safety and effectiveness of the combination. The blood samples were collected and analyzed for estimation of blood glucose levels by GOD/POD method and serum pioglitazone levels by HPLC method for pharmacokinetic data. The olanzapine alters the pharmacokinetics of pioglitazone and found to enhance the hypoglycaemic effect pioglitazone. Olanzapine appears to produce pharmacokinetic interaction with pioglitazone which might be by inhibiting the metabolism of pioglitazone.

Keywords: Pioglitazone, olanzapine, diabetes, Pharmacokinetic and pharmacodynamic drug interaction

A R T I C L E I N F O

CONTENTS

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1. Introduction

The study of mechanisms of drug interaction is of much value in selecting drug concentrations to provide rational therapy. Drug interaction studies assume much importance, especially for drugs that have a narrow margin of safety,

and where the drugs are used for a prolonged period of time. Diabetes mellitus is one such metabolic disorder that needs treatment for prolonged periods, and maintenance of normal blood glucose level is very important in this condition, since both hyperglycemia, as well as hypoglycemia is unwanted phenomenon [1].

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels and disturbances in carbohydrate, fat and protein metabolism, and an increased risk of complications from vascular disease. Diabetes may be due to a decrease in the synthesis of insulin (type-1) or a decrease in the secretion of insulin (type-2) from the ß-cells of islets of langerhans of the pancreas. There are estimated 143 million people worldwide sufferings from diabetes [2] and the number may well double by the year 2030 [3]. In India, the prevalence rate of diabetes is estimated to be 1–5%.

The occurrence of diabetes in psychiatric diseases is two to four times more than normal groups, which leads to drug-drug interaction during the treatment [4]. Oral hypoglycemic agents are used in the treatment of type-2 diabetes, pioglitazone is a prescription drug of the thiazolidinedione (TZD) class used to treat diabetes. Pioglitazone is known to act by stimulating the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α. Olanzapine is an atypical antipsychotic used to treat in psychiatric diseases. Pioglitazone and olanzapine both are metabolized by Cytochrome P 450 system. Since there is every possibility for the combined use of pioglitazone and olanzapine in chronic diabetics with associated psychiatric diseases, the study is planned to investigate the effect of olanzapine on the activity of pioglitazone in normal and diabetic rats, to evaluate the safety and effectiveness of the combination. Also the study is planned to find the pharmacodynamics and pharmacokinetics of pioglitazone in the presence of olanzapine in rabbits, to evaluate the mechanisms of interaction if they occur.

2. Materials and Methods

2.1 Drugs and chemicals:

Pioglitazone and olanzapine are gift samples from Dr. Reddys laboratories (Hyderabad, India). Alloxan monohydrate was purchased from LOBA Chemie (Mumbai, India). Glucose kits (Erba) were purchased from a local pharmacy. All other reagents used were of an analytical grade.

2.2 Experimental animals:

Albino rats of either sex, 6–7 weeks of age, weighing between 250 to 320 g, and normal albino rabbits of either sex of 3 months of age, weighing between 1.35 to 1.75 Kg, were used in the study. They were procured from the Raghavendra enterprises, Bangalore, India. They were maintained under standard laboratory conditions at an ambient temperature of 25 ± 2 C and 50 ± 15% relative humidity, with a 12-h light/12-h dark cycle. Animals were fed with a commercial pellet diet) and water *ad libitum*. They were fasted for 18 h prior to the experiment, and during the experiment, the food and water were withdrawn. The animal experiments were performed after prior approval of the study protocol by the Institutional Animal Ethics Committee and by the Government regulatory body for animal research. (Reg. No.878/ac/05/CPCSEA/ 003/ 2013). The study was conducted in accordance with the guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

2.3. Selection of doses and preparation of oral test suspension: In clinical practice, olanzapine and pioglitazone in a therapeutic dose will be administered orally as antipsychotic and antidiabetic therapy, respectively. Human oral therapeutic doses of the respective drugs were extrapolated to rat/rabbit based on body surface area [5]. But the dose of pioglitazone for rat experiments was selected as 10 mg/kg bd. wt. based on the influence of dose effect-relationship of pioglitazone on blood glucose in normal rats. Olanzapine and pioglitazone was suspended in 2% CMC-Na for oral administration. All the drugs were administered to the respective groups by oral gavage.

2.4. Pharmacodynamic interaction study in normal and diabetic rats:

A group of six normal rats was administered with of pioglitazone, orally. The same group was administered with olanzapine, orally and the combination of pioglitazone and olanzapine. One week washout period was maintained between treatments. After this single dose interaction study, the same group was continued with the daily treatment of interacting drug (olanzapine) for the next 8 days with regular feeding. Later after 18 h fasting, they were again given the combined treatment on the 9th day. The same treatment (single dose followed by multiple dose interaction study) was repeated in a group of six alloxan-induced diabetic rats. Diabetes was induced in rats by the administration of alloxan monohydrate in two doses, i.e. 100 mg and 50 mg/kg bd. wt. intraperitonially for two consecutive days [6]. After 72 h, samples were collected from rats by orbital puncture of all surviving rats, and the serum was analysed for glucose levels. Rats with blood glucose levels of 200 mg/dl and above were considered as diabetic and selected for the study.Blood samples were withdrawn from retro orbital plexus [7] of each rat at 0, 1, 2, 3, 4, 6, 8 and 12 h. These blood samples were analysed for blood glucose by GOD/POD method [8] using commercial glucose kits.

2.5. Pharmacodynamic and pharmacokinetic interaction study in rabbits: A group of five rabbits was administered with pioglitazone, orally. The same group was administered with olanzapine, orally and the combination of olanzapine and pioglitazone. One week washout period was maintained between treatments. After this single dose interaction study the same group was continued with the daily treatment of interacting drug (olanzapine) for the next 8 days with regular feeding. Later after 18 h fasting they were again given the combined treatment on the 9th day. Blood samples were withdrawn from the marginal ear vein of each rabbit at 0, 1, 2, 4, 6, 8, 12, 18, and 24 h. These blood samples were analysed for blood glucose by GOD/POD method using commercial glucose kits. The serum

pioglitazone concentrations were determined by HPLC method. The pharmacokinetic parameters of pioglitazone were determined on subjecting the concentration-time data to non-compartmental analysis using Win Nonlin (Version 5.0.1) Software.

2.6. Data and statistical analysis:

Data were expressed as mean ± SEM. The significance was determined by applying Student's paired t - test.

3. Results and Discussion

3.1. Pharmacodynamic interaction study in normal and diabetic rats: Pioglitazone produced hypoglycemic activity with maximum reduction of 23.47±0.47% in normal rats, and 38.76±1.05% in diabetic rats at 2 h. Olanzapine has no significant effect on the blood glucose levels in normal and diabetic rats. In combination, olanzapine produced enhanced hypoglycemic effect of pioglitazone with maximum blood glucose reduction of 26.32±0.89% and 28.59±1.13% at 2 h, following single dose and multiple dose administration of olanzapine, respectively, in normal rats (Table 1). In combination, olanzapine produced enhanced hypoglycemic effect of pioglitazone with maximum blood glucose reduction of 41.03±0.93% and 44.30±0.80% at 2 h, following single dose and multiple dose administration of olanzapine, respectively, in diabetic rats (Table 2). The enhancement in pioglitazone effect is more with the multiple dose treatment of Olanzapine than single dose treatment.

3.2. Pharmacodynamic interaction study in normal rabbits: Pioglitazone produced hypoglycemic activity with maximum reduction of 37.41±0.60% at 4 h in normal rabbits. Olanzapine has no significant effect on the blood glucose levels in normal rabbits. Olanzapine produced enhanced hypoglycemic effect of pioglitazone with maximum reduction of 45.39±0.81% and 48.85±0.78% in the blood glucose in normal rabbits at 4 h following single dose and multiple dose treatment of olanzapine, respectively (Table 3). The enhancement in pioglitazone effect is more with the multiple dose treatment of olanzapine than the single dose treatment.

3.3. Pharmacokinetic interaction study in normal rabbits: The serum pioglitazone levels were increased (Table 4), and pharmacokinetic parameters of pioglitazone like Cmax, Tmax, AUC, AUMC, and T1/2 were altered significantly with single- and multiple-dose treatments of olanzapine in normal rabbits (Table 5).

Discussion

Drug interactions are usually seen in clinical practice, and the mechanisms of interactions are evaluated usually in animal models (rodent and non-rodent). We studied the influence of olanzapine on the pharmacodynamics and pharmacokinetics of pioglitazone in rats (rodents) and rabbits (non-rodent). The normal rat model served to quickly identify the interaction and the diabetic rat model served to validate the same response in the actually used condition of the drug. The rabbit model is another dissimilar species to validate the occurrence of the interaction. The multiple dose effect of olanzapine on pioglitazone activity was also studied for the influence of long term treatment with olanzapine, since both are used for chronic period. So we have conducted the dose effect-relationship study of pioglitazone to select the oral dose. In our study, olanzapine alone did not produce any significant activity on blood glucose levels of rats (normal and diabetic) and rabbits. Interestingly, however, the pioglitazone hypoglycemic activity was significantly enhanced by olanzapine, following a single and multiple dose treatment in rat and rabbit models, and this confirmed the presence of potential interaction between pioglitazone and olanzapine. It is clear that since olanzapine did not alter blood glucose levels on its own, the increase in the effect of pioglitazone on blood glucose may be due to improved blood pioglitazone level in the presence of olanzapine, as it was confirmed by pharmacokinetic interaction study in rabbits. There was a significant rise in serum pioglitazone levels and an alteration in pharmacokinetic parameters like Cmax, Tmax, AUC, AUMC, and T1/2 of pioglitazone with single- and multiple-dose treatments of olanzapine. The increase in AUC and AUMC indicates improved availability of pioglitazone in presence of olanzapine. The altered T1/2 indicates alteration either in metabolism or the excretion process, further increase in Cmax and AUC might be due to enhancement of absorption of pioglitazone in the presence of olanzapine, a known p-glycoprotein inhibitor.

Table 1: Effect of single and multiple dose treatments of olanzapine on pioglitazone blood glucose levels in normal rats.

Time (h)	Percent blood glucose reduction			
	Pioglitazone alone	Olanzapine alone	Olanzapine +Pioglitazone (SD)	Olanzapine +Pioglitazone (MD)
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	12.03±0.43	3.53±0.77	13.05±1.19	14.75±1.19
2	23.47±0.47	6.76±0.59	26.32±0.89	28.59±1.13*
3	18.17±0.33	5.34±0.60	18.39±1.46	19.88±1.58
4	14.35±0.60	4.53±0.59	13.24±0.67	14.77±1.32
6	10.98±0.48	3.69±0.60	9.83±0.41	11.06±1.42
8	7.79±0.65	3.29±0.47	6.62±0.57	7.48±1.43
10	4.61±0.59	2.48±0.61	4.53±0.69	5.56±1.14
12	1.88±0.31	1.66±0.58	3.59±0.98	2.78±0.67

*Significant at $P < 0.05$ compared to pioglitazone control.

Table 2: Effect of single and multiple dose treatments of olanzapine on pioglitazone blood glucose levels in diabetic rats

Time (h)	Percent blood glucose reduction			
	Pioglitazone alone	**Olanzapine alone**	**Olanzapine +Pioglitazone (SD)**	**Olanzapine +Pioglitazone (MD)**
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	26.09±0.92	4.55±0.54	29.47±0.52	31.70±0.52*
2	38.76±1.05	9.29±0.64	41.03±0.93*	44.30±0.80*
3	32.27±0.78	7.60±0.52	36.46±0.90	39.80±0.92*
4	27.02±0.66	5.83±0.57	31.04±0.81	33.61±0.75*
6	22.44±0.54	4.15±0.46	25.53±1.01	27.81±0.74*
8	18.29±0.40	3.09±0.40	21.35±1.30	23.99±1.09
10	14.72±0.40	2.16±0.41	16.12±0.97	18.23±0.56
12	10.92±0.42	1.13±0.40	12.71±1.10	15.32±0.81

*Significant at P < 0.05 compared to pioglitazone control.

Table 3: Effect of single and multiple dose treatments of olanzapine on pioglitazone blood glucose levels normal rabbits

Time (h)	Percent blood glucose reduction			
	Pioglitazone alone	**Olanzapine alone**	**Olanzapine +Pioglitazone (SD)**	**Olanzapine +Pioglitazone (MD)**
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	22.56±1.05	3.06±0.62	28.62±2.34*	26.61±1.43*
2	30.02±1.00	7.01±1.04	38.54±1.32*	38.47±2.76*
4	37.41±0.60	9.46±0.40	45.39±0.81*	48.85±0.78*
6	29.93±0.48	8.20±0.53	38.16±0.64*	43.73±0.33*
8	23.60±0.27	7.18±0.80	30.85±1.09*	39.32±0.72*
12	17.31±1.05	4.27±1.09	22.86±0.88*	35.27±0.68*
18	12.05±0.90	2.87±0.88	18.20±1.69*	31.76±0.50*
24	7.56±1.17	1.83±0.86	13.24±1.20*	21.14±1.24*

* Significant at P < 0.05 compared to pioglitazone control.

Table 4: Mean Serum pioglitazone levels with pioglitazone alone and in combination with olanzapine single and multiple dose treatments in rabbits

Time (h)	Serum pioglitazone levels (µg/ml)		
	Pioglitazone alone	**Pioglitazone + Olanzapine (SD)**	**Pioglitazone + Olanzapine (MD)**
0	0.00±0.00	0.00±0.00	0.00±0.00
1	2.92±0.25	4.12±0.10	4.28±0.16
2	7.61±0.36	9.04±0.15	9.75±0.22
4	11.83±0.24	14.17±0.18*	14.11±0.36*
6	8.98±0.35	12.00±0.35*	11.52±0.26*
8	7.22±0.23	9.78±0.23	10.07±0.13*
12	5.45±0.25	7.95±0.28	8.19±0.21*
18	2.83±0.31	5.87±0.10	5.92±0.10*
24	1.17±0.17	3.82±0.17	3.71±0.19

* Significant at P < 0.05 compared to pioglitazone control

Table 5: Pharmacokinetic parameters of pioglitazone before and after administration of olanzapine

Pharmacokinetic parameters	**Pioglitazone**	**Pioglitazone+ Olanzapine (SD treatment)**	**Pioglitazone+ Olanzapine (MD treatment)**
AUC_{0-24}(µg/ml /h)	125.31±4.47	185.82±2.49	187.97±1.85
$AUC_{0-\alpha}$ (µg/ml/h)	136.29±6.69	246.47±4.68	247.51±5.85
$AUMC_{0-24}$ (µg/ml/h*h)	1032.17±110.86	2541.22±67.56	2519.96±66.29
$AUMC_{0-\alpha}$ (µg/ml/h*h)	1400.09±197.62	4966.26±299.47	4909.26±301.35
Ka (h^{-1})	1.15±0	1.15±0.00	1.15±0.00
T1/2 (h)	6.26±0.39	10.94±0.42	11.03±0.45
Vdss	446.35±20.71	518.62±17.83	507.74±12.89
Cl	67.33±4.41	27.05±0.51	26.96±0.68

T_{max} (h)	4.00±0.00	4.00±0.00	4.00±0.00
C_{max} (µg/ml)	11.83±0.24	14.17±0.18	14.11±0.36
MRT (h)	10.10±0.88	20.10±0.90	19.77±0.81

4. Conclusion

The interaction appears to be pharmacokinetic interaction at absorption and metabolic level. Since the interaction was seen in two dissimilar species, it is likely to occur in humans also leading to increased activity of pioglitazone, which may need dosage adjustment. Hence, care should be taken when the combination is prescribed for clinical benefit in diabetic patients. However, the present study warrants further studies to find out the relevance of this interaction in human beings.

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