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Pharmacokinetic Drug Interaction of Quetiapine and 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 quetiapine 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 quetiapine alters the pharmacokinetics of pioglitazone and found to enhance the hypoglycaemic effect pioglitazone. Quetiapine appears to produce pharmacokinetic interaction with pioglitazone which might be by competitive antagonisms of its metabolism by inhibiting CYP 3 A4 isozyme and/or by enhancing pioglitazone absorption by inhibiting the P-glycoprotein.

Keywords: Pharmacokinetic drug interaction, Quetiapine, Pioglitazone

A R T I C L E I N F O

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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. Quetiapine is an atypical antipsychotic used to treat in psychiatric diseases. Pioglitazone and quetiapine both are metabolized by Cytochrome P 450 system particularly CYP 3A4. Since there is every possibility for the combined use of pioglitazone and quetiapine in chronic diabetics with associated psychiatric diseases, the study is planned to investigate the effect of quetiapine 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 quetiapine in rabbits, to evaluate the mechanisms of interaction if they occur.

2. Materials and Methods

2.1 Drugs and chemicals:

Pioglitazone and quetiapine 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, quetiapine 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. Quetiapine 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 quetiapine, orally and the combination of pioglitazone and quetiapine. 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 (quetiapine) 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 quetiapine, orally and the combination of quetiapine 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 (quetiapine) 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 WinNonlin (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 discussions

3.1. Pharmacodynamic interaction study in normal and diabetic rats: Pioglitazone produced hypoglycemic activity with maximum reduction of 23.67±0.65% in normal rats, and 38.06±0.87% in diabetic rats at 2 h. Quetiapine has no significant effect on the blood glucose levels in normal and diabetic rats. In combination, quetiapine produced enhanced hypoglycemic effect of pioglitazone with maximum blood glucose reduction of 33.76±1.05% and 36.74±0.60% at 2 h, following single dose and multiple dose administration of quetiapine, respectively, in normal rats (Table 1). In combination, quetiapine produced enhanced hypoglycemic effect of pioglitazone with maximum blood glucose reduction of 42.26±1.28% and 45.18±0.54% at 2 h, following single dose and multiple dose administration of quetiapine, respectively, in diabetic rats (Table 2). The enhancement in pioglitazone effect is more with the multiple dose treatment of Quetiapine than single dose treatment.

3.2. Pharmacodynamic interaction study in normal rabbits: Pioglitazone produced hypoglycemic activity with maximum reduction of 34.69±0.50% at 4 h in normal rabbits. Quetiapine has no significant effect on the blood glucose levels in normal rabbits. Quetiapine produced enhanced hypoglycemic effect of pioglitazone with maximum reduction of 44.15±0.62% and 48.29±1.00% in the blood glucose in normal rabbits at 4 h following single dose and multiple dose treatment of quetiapine, respectively (Table 3). The enhancement in pioglitazone effect is more with the multiple dose treatment of quetiapine 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 quetiapine 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 quetiapine 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 quetiapine on pioglitazone activity was also studied for the influence of long term treatment with quetiapine, since both are used for chronic period. Rats are known to be more sensitive to pioglitazone response. So we have conducted the dose effect-relationship study of pioglitazone to select the oral dose. In our study, quetiapine 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 pioglitazone, following a single and multiple dose treatment in rat and rabbit models, and this confirmed the presence of potential interaction between pioglitazone and quetiapine. It is clear that since quetiapine 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 quetiapine, 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 quetiapine. The increase in AUC and AUMC indicates improved availability of pioglitazone in presence of quetiapine. The altered T1/2 indicates alteration either in metabolism or the excretion process. Quetiapine and pioglitazone are metabolized by Cytochrome P450 system particularly with CYP 3A4 and there is more possibility of quetiapine for alteration of metabolism of pioglitazone. Further increase in Cmax and AUC might be due to enhancement of absorption of pioglitazone in the presence of quetiapine, a known p-glycoprotein inhibitor [9].

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

Time (h)	Percent blood glucose reduction			
	Pioglitazone alone	**Quetiapine alone**	**Quetiapine +Pioglitazone (SD)**	**Quetiapine +Pioglitazone (MD)**
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	12.37±0.53	9.27±0.46	21.73±0.85*	24.16±0.65*
2	23.67±0.65	13.93±0.92	33.76±1.05*	36.74±0.60*
3	19.05±0.71	12.23±0.42	26.84±1.95*	29.72±1.37*
4	15.70±0.62	9.97±0.68	21.98±1.92*	25.15±1.93*
6	12.34±0.86	7.85±0.88	16.14±1.36	19.73±1.59*
8	8.17±0.56	5.97±0.86	11.67±0.96	15.14±1.44*
10	5.02±0.67	4.30±0.61	8.57±1.09	11.21±1.30*

12	1.87±0.45	2.00±0.36	6.62±0.78*	8.20±1.41*

*Significant at P < 0.05 compared to pioglitazone control.

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

Time (h)	Percent blood glucose reduction			
	Pioglitazone alone	Quetiapine alone	Quetiapine +Pioglitazone (SD)	Quetiapine +Pioglitazone (MD)
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	24.60±0.82	14.02±1.07	33.44±1.20	36.83±0.74*
2	38.06±0.87	19.86±0.56	42.26±1.28	45.18±0.54*
3	32.29±1.21	16.00±0.59	36.66±1.13	38.79±0.75*
4	27.07±0.92	12.85±0.42	30.83±1.04	33.17±0.86*
6	23.00±0.46	10.87±0.31	26.23±1.22	27.99±0.97*
8	17.95±0.53	7.68±0.69	21.88±1.58	23.27±1.32
10	15.16±0.42	5.56±0.57	16.51±1.59	17.06±1.62
12	11.74±0.53	4.09±0.66	13.43±0.97	12.87±1.11

*Significant at P < 0.05 compared to pioglitazone control.

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

Time (h)	Percent blood glucose reduction			
	Pioglitazone alone	Quetiapine alone	Quetiapine +Pioglitazone (SD)	Quetiapine +Pioglitazone (MD)
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	20.32±0.58	10.94±0.71	28.32±1.01*	28.82±0.68*
2	26.46±0.68	15.06±0.56	40.24±0.55*	42.70±1.21*
4	34.69±0.50	13.35±0.47	44.15±0.62*	48.29±1.00*
6	27.05±0.71	11.61±0.35	37.43±0.48*	44.11±0.51*
8	20.72±1.15	9.48±0.38	33.29±1.24*	37.58±0.56*
12	15.42±0.69	7.53±0.88	29.58±1.10*	32.46±1.12*
18	11.80±0.51	4.84±0.72	26.22±1.51*	27.85±1.33*
24	8.62±0.65	1.43±0.65	21.31±1.83*	23.24±1.63*

*Significant at P < 0.05 compared to pioglitazone control.

Table 4: Serum pioglitazone levels in rabbits

Time (h)	Serum pioglitazone levels (µg/ml)		
	Pioglitazone alone	Pioglitazone + Quetiapine (SD)	Pioglitazone + Quetiapine (MD)
0	0.00±0.00	0.00±0.00	0.00±0.00
1	3.15±0.12	5.88±0.13	5.97±0.13
2	7.87±0.19	12.09±0.22*	12.52±0.28*
4	12.32±0.27	18.73±0.32*	19.09±0.38*
6	9.59±0.35	15.65±0.40*	16.33±0.47*
8	7.86±0.33	12.62±0.33*	12.97±0.39*
12	6.00±0.17	10.60±0.21*	11.39±0.26*
18	3.06±0.24	8.12±0.13*	8.76±0.28*
24	1.07±0.09	5.12±0.21*	5.07±0.15*

*Significant at P < 0.05 compared to pioglitazone control.

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

Pharmacokinetic parameters	Pioglitazone	Pioglitazone + Quetiapine (single dose treatment)	Pioglitazone + Quetiapine (Multiple dose treatment)
AUC_{0-24}(µg/ml /h)	133.95±3.73	247.70±3.95	259.23±5.11
$AUC_{0-\alpha}$(µg/ml/h)	143.29±4.10	332.48±8.25	342.24±8.60
$AUMC_{0-24}$(µg/ml/h*h)	1053.81±65.34	3453.12±80.01	3572.46±104.47
$AUMC_{0-\alpha}$(µg/ml/h*h)	1360.04±99.06	6893.75±283.12	6925.98±268.08
Ka (h^{-1})	1.15±0.00	1.15±0.00	1.15±0.00
T1/2 (h)	5.97±0.23	11.45±0.23	11.34±0.19
Vdss	399.19±20.01	397.46±5.33	376.74±5.32

Cl	46.61±1.33	20.07±0.49	19.50±0.46
T_{max} (h)	4.00±0.00	4.00±0.00	4.00±0.00
C_{max} (µg/ml)	12.32±0.27	18.73±0.32	19.09±0.38
MRT (h)	9.46±0.51	20.70±0.38	20.21±0.30

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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