International Journal of Chemistry and Pharmaceutical Sciences

Journal Home Page: www.pharmaresearchlibrary.com/ijcps

Research Article **Open Access**

Pharmacodynamic and Pharmacokinetic Drug Interaction of Risperidone with Pioglitazone

Bhupalam Pradeep kumar*[1], Y. Padmanabha Reddy[2], N. Devanna[3]

[1]*Department of Pharmacology, Center for Pharmaceutical Research, Raghavendra Institute of Pharmaceutical Education and Research, Anantapuramu-515721, Andhra Pardesh, India.*
[2]*Principal, Raghavendra Institute of Pharmaceutical Education and Research, Anantapuramu-515721, A.P, India.*
[3]*Principal, JNTUA College of Engineering, Kalikiri-515234, Andhra Pardesh, India.*

A B S T R A C T

The present study was performed to investigate the effect of risperidone on the pharmaco dynamic and pharmacokinetics of pioglitazone 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 as well as Pioglitazone was estimated for pharmacokinetic data. The risperidone alters the pharmacokinetics of pioglitazone and produces hypoglycaemic effect. Risperidone appears to produce interaction with pioglitazone by pharmacokinetic and pharmacodynamic mechanisms.

Keywords: risperidone, pharmacokinetics, pioglitazone.

A R T I C L E I N F O

CONTENTS

1. Introduction 37
2. Materials and Methods. 38
3. Results and Discussion. 38
4. Mechanism 40
5. References 40

Article History: Received 15 October 2015, **Accepted** 28 November 2015, **Available Online** 27 January 2016

***Corresponding Author**
Bhupalam Pradeep kumar
Dept. of Pharmacology, Center for Pharmaceutical Research, Raghavendra Institute of Pharmaceutical Education and Research, Anantapuramu-515721, Andhra Pradesh, India. Manuscript ID: IJCPS2809

PAPER-QR CODE

Citation: Bhupalam Pradeep kumar, *et al.* Pharmacodynamic and Pharmacokinetic Drug Interaction of Risperidone with Pioglitazone. *Int. J. Chem, Pharm, Sci.*, 2016, 4(1): 37-40.

1. Introduction

Now a day's use of more than one drug (Poly pharmacy) is a common practice to treat the chronic disorders like diabetes mellitus. Poly pharmacy is quite common practice all over the world to treat single disorder and multiple

disorders which occur simultaneously. [4] In such a situation one drug may interact with other drug leading to drug -drug interactions. Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia; it needs treatment for prolonged period. 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. [1] To study such drug interactions this work is being carried out.

2. Materials and Methods

Experimental animals:

Albino rabbits of either sex weighing between 1.5 to 2 Kg were selected; they were housed in well ventilated aluminium cages individually. They were maintained on uniform diet and temperature with 12 h light and dark cycles. Standard animal pellet food was provided in adequate quantity with drinking water *ad libitum.* Set of 6 rabbits were used for finding the influence of risperidone on blood glucose levels and pharmacokinetic parameters of pioglitazone.

Single dose studies:

The rabbits were fasted for 18 hrs prior to experiment with water *ad libitum*. During experimentation water also withdrawn. The blood was drawn from marginal ear vein in small plastic disposable centrifuge tubes containing a small quantity of powdered anti coagulant. The blood samples were centrifuged and blood glucose was estimated by GOD/POD method at intervals of 0, 1, 2, 4, 6, 8, 12, 18, and 24 hrs. This stage served as control without any drug treatment. After four days the same group was treated with therapeutic dose of risperidone. The dosage of drugs administered orally was decided upon human therapeutic dose extended to animals as suggested by Laurence and Bacharach. [2] The drugs were administered orally with the help of an oral gag using a soft rubber catheter of 5 mm diameter as described by Ghosh M.N. [3] after the administration of therapeutic dose of risperidone, the blood samples were collected and glucose was estimated at pre determined intervals of time. Later the rabbits were left for a washout period. Therapeutic dose of pioglitazone was administered orally and blood samples were collected and glucose as well as pioglitazone levels were estimated in blood at pre determined time intervals for 24 hrs. After a wash out period of 4 days, the therapeutic dose of risperidone was administered first, followed by therapeutic dose of pioglitazone after an interval of 30 min orally. The blood samples were collected and glucose as well as pioglitazone level were estimated at pre determined time intervals as described above. The pharmacokinetic parameters like AUC, AUMC, Cmax, Tmax, and MRT were calculated for the above data for all sets of experiments. The results were calculated by student's t-test.

Multiple dose studies:

For studying the influence of multiple dose treatment, another set of 6 normal rabbits was selected and drugs were administered orally .The experimental conditions and protocols were identical. The experiments were designed to collect pharmacodynamic as well as pharmacokinetic data from the study by estimating glucose level as well as pioglitazone levels from the blood. In these experiments therapeutic dose of risperidone and therapeutic dose of pioglitazone was administered orally with gap of 30 min after 18 h fast. Later they were treated daily with therapeutic dose of risperidone for the next 8 days with regular feeding. On 9th day after 18 h fast they were again given the combined treatment with risperidone and pioglitazone with 30 min gap. The blood samples were collected at specified intervals, and blood glucose (GOD/POD) and blood pioglitazone levels were estimated.

Insulin estimation:

Three rabbits were used for estimating insulin levels for finding the influence of risperidone, the rabbits were housed in well ventilated aluminium cages individually .The experimental protocols were similar as described above. The blood samples were collected at zero hour, peak hr of the activity and at the terminal stage of elimination of drug from each rabbit for both glucose as well as insulin estimation.

3. Results and Discussion

Results

The result of the study as shown in tables 1 to 6. Risperidone has been found to enhance the hypoglycaemic effect of pioglitazone. The peak hypoglycaemic effect of pioglitazone as well as that of the combination had correspondingly maximum concentration of pioglitazone levels in the blood. The studies indicate that pioglitazone levels were raised in the presence of risperidone at 2 hours by partial inhibition of pioglitazone metabolism. Pioglitazone and risperidone are metabolised by CYP-3A4 which might be responsible for effect on pioglitazone metabolism and action. The AUC and AUMC values were increased in combination group from 3095 ng/ml/hr and 28690 ng/ml/hr to 8790 ng/ml/hr and 67220 ng/ml/hr respectively.

Compared to only pioglitazone treated group indicating better availability for pioglitazone in presence of risperidone the Cmax value of pioglitazone increased from 2092 ng/ml to 4185 ng/ml indicating enhanced distribution of pioglitazone in presence of risperidone. However the Tmax remain unaltered at 2nd hour. The mean residence time was increased in combination group from 11.67 hours to 21.5 hours when compared with only pioglitazone treated group. The results of multiple dose influence of risperidone on pioglitazone kinetics indicate that the peak hour of the activity of drug was 2 hr, both on first day as well as 9th day. There was no significant difference between single dose treatment and multiple dose treatment of risperidone on pharmacokinetics and hypoglycaemia of pioglitazone. The student's t-test for paired data indicates statistically significant difference in pharmacological response between pioglitazone alone and combination of pioglitazone and risperidone. In insulin estimation studies average blood glucose levels where 89.82mg,60.23mg and 82.6mg/dl respectively at zero hour, peak hour (2hrs) and at the terminal stage of drug elimination(12hrs).The average insulin levels as Micro I.U /ml. Were 2.49, 5.72 and 2.69 respectively.

Discussion

The risperidone enhanced pioglitazone hypoglycaemia on co administration may be because of their added pharmacological effect additionally it may inhibit hepatic metabolism of pioglitazone, which is metabolised by cyp 3A4 enzymes. The pancreatic beta cells over production of insulin due to ATP sensitive potassium channel inhibition are also responsible for the hypoglycaemic effect. The improved blood levels with consequent improved hypoglycaemia of pioglitazone in combination may be another reason when it was administered with risperidone. The blood glucose and blood pioglitazone levels in the presence and absence of risperidone indicate the involvement of pharmacodynamic as well as pharmacokinetic mechanisms.

The risperidone is metabolised by CYP-3A4 isoenzyme and pioglitazone is metabolised by CYP-2C9 and CYP-3A4 and excreted in urine. Thus risperidone is likely to inhibit the pioglitazone metabolism leading to an enhanced pioglitazone blood levels altering the ADME pathways. The results indicate that risperidone increases insulin secretion, which in turn is responsible for its hypoglycaemic effect. Thus risperidone appears to produce interaction by pharmacokinetic and pharmacodynamic mechanisms. The studies with interaction between risperidone and pioglitazone indicate that simultaneous use of risperidone and pioglitazone need careful monitoring of blood glucose with dosage adjustment of pioglitazone.

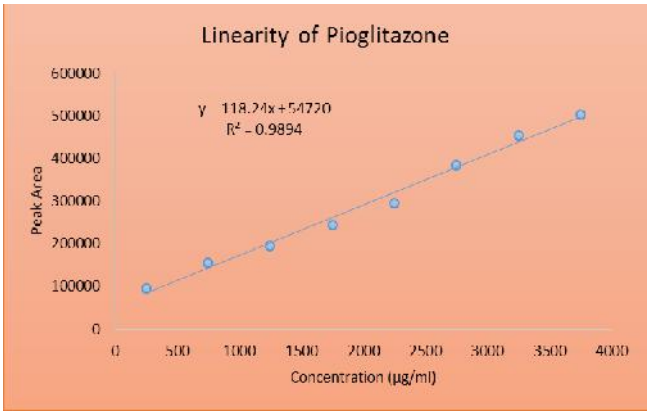

Figure 1: Standard graph of pioglitazone

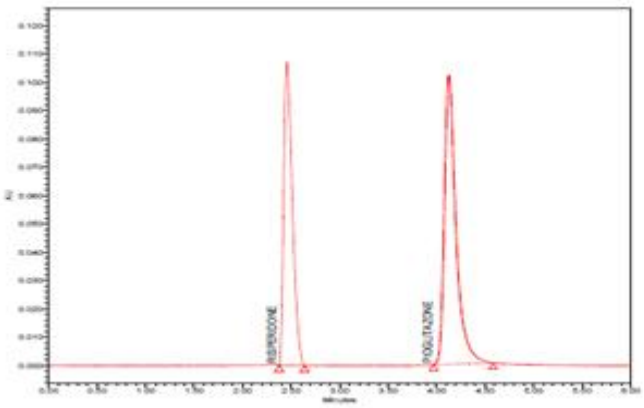

Figure 2: Pioglitazone Chromatogram

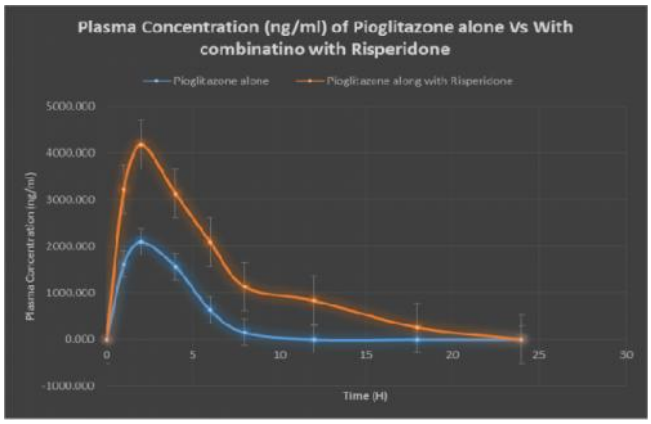

Figure 3: Plasma concentration of pioglitazone alone Vs in combination with risperidone

Table1: Mean plasma Pioglitazone concentrations of single dose study

Time (hr)	Pioglitazone(ng/ml)	Pioglitazone + Risperidone (ng/ml)
0	0.000	0.000
1	1612.465±0.85	3224.931±0.65
2	2092.373±0.63	4184.745±0.17
4	1561.052±0.78	3122.104±0.98
6	627.621±0.14	2088.575±0.17
8	148.746±0.96	1130.826±0.27
12	0.000	831.729±0.36
18	0.000	260.197±0.17
24	0.000	0.000

Table 2: Pharmacokinetic parameters of pioglitazone after single dose study

PK Parameters	Pioglitazone	Pioglitazone+ Risperidone
AUC_{0-t} (ng/ml/h)	3095±33.01	8790 ± 83.94***
$AUMC_{0-t}$ (ng/ml/h*h)	28690 ± 253.6	67220 ± 989.0 ***
$AUC_{0-\infty}$	3685 ± 51.61	5546 ± 134.1 ***
$AUMC_{0-\infty}$	28870 ±264.2	44290 ± 2345 ***
C_{max} (ng/ml)	2092± 8.728	4185 ± 17.46 ***
T_{max} (h)	2	2
Abs $t_{1/2}$ (h)	1.05±0.0	1.05±0.0
MRT (h)	11.67±0.3437	21.50 ± 0.3045 ***

n=6, P* <0.05, P** <0.01, P*** <0.001

Table3: Mean plasma Pioglitazone concentrations of multiple dose study

Time (hr)	Pioglitazone (ng/ml)	Pioglitazone+ Risperidone (ng/ml)
0	0.000	0.000
1	1433.507±0.63	3650.546±1.69
2	2076.061±0.45	4697.633±1.78
4	1871.677±0.36	3346.489±1.2
6	909.701±0.05	2284.12±1.36
8	494.037±0.96	1146.337±1.0
12	169.997±0.50	684.915±1.63
18	0.000	174.495±0.24
24	0.000	0.000

Table 4: Pharmacokinetic parameters of pioglitazone after multiple dose study

PK Parameters	Pioglitazone	Pioglitazone + Risperidone
AUC_{0-t} (ng/ml/h)	2756 ± 21.18	8506 ± 81.45 ***
$AUMC_{0-t}$ (ng/ml/h*h)	34400 ± 373.9	73590 ± 660.2 ***
$AUC_{0-\infty}$	39630 ± 456.8	42390 ± 625.3 ***
$AUMC_{0-\infty}$	44860 ± 540.2	47560 ± 237.2 ***
C_{max} (ng/ml/)	2076 ± 25.93	4698 ± 54.73 ***
T_{max} (h)	2	2
Abs $t_{1/2}$ (h)	1.03±0.0	1.04±0.0
MRT (h)	10.89 ± 0.2340	21.68 ± 0.5043 ***

n=6, P* <0.05, P** <0.01, P*** <0.001

Table 5: Mean percent blood glucose reduction by risperidone, pioglitazone & their combination in single dose study

Group	percent blood glucose reduction ± SEM								
	Time (h)								
	0	1	2	4	6	8	12	18	24
Control	0.00	1.07± 0.82	1.15± 1.84	5.85± 0.80	8.03± 1.38	11.24± 1.50	12.75± 2.05	13.16± 1.67	15.26± 0.72
Pioglitazone	0.00	41.04± 2.61	43.38± 2.99	44.45± 1.96	38.17± 1.71	37.52± 2.18	34.67± 1.78	23.45± 21.21	11.33± 1.80
Risperidone	0.00	2.07± 1.22	2.34± 1.59	5.04± 1.50	9.06± 2.21	12.61± 1.87	13.20± 1.55	15.91± 0.88	17.49± 2.51
Pioglitazone +Risperidone	0.00	52.08± 0.69**	54.47± 2.53*	49.93± 1.86	40.82± 2.03	39.43± 2.19	38.41± 1.95	29.26± 1.87	23.40± 1.82**

n=6, P* <0.05, P** <0.01, P*** <0.001

Table 6: Mean percent blood glucose reduction by risperidone, pioglitazone& their combination in multiple dose study

Group	percent blood glucose reduction ± SEM								
	Time (h)								
	0	1	2	4	6	8	12	18	24
Control	0.00	1.68± 1.37	0.82± 1.26	4.12± 0.71	8.14± 1.06	8.27± 0.53	10.97± 1.58	16.55± 2.86	19.42± 3.43
Piog	0.00	41.20± 2.62	43.81± 3.02	49.42± 2.18	40.29± 2.64	37.76±2 .17	35.64± 2.11	26.80± 2.07	17.65± 2.35
Risperidone	0.00	2.34± 2.17	4.52± 5.48	8.21± 2.36	11.50± 3.09	13.01±3 .22	14.57± 1.50	17.90± 2.51	20.50± 2.61
Pioglitazone+ Risperidone	0.00	49.45± 1.25*	55.83± 3.49*	50.12± 1.81	37.67± 1.33	39.93±0 .93	32.96± 2.89	28.55± 1.99	23.74± 2.89

n=6, P* <0.05, P** <0.01, P*** <0.001

4. Conclusion

Simultaneous use of risperidone and pioglitazone need careful monitoring of blood glucose with dosage adjustment of pioglitazone.

5. References

[1] Yatan pal singh balhara. Diabetes and psychiatric disorders. *Indian journal of endocrinology & metabolism*. **2011**, 15 (4): 274-283.

[2] Laurence DR Bacharch AL. Evaluation of drug activities and pharmacometrics. London and New York: Academic press; **1964**: 161.

[3] Ghosh MN. Fundamentals of experimental pharmacology. 1st ed. Calcutta: Scientific book agency. **1971**: 6.

[4] Satyanarayana S, Nitin M, Prasad K. Pharmacodynamic and pharmacokinetic drug interaction of Mexiletine with tolbutamide in rabbits. *Indian journal of pharmaceutical education and research*. **2011**. 45(1): 40-45.

[5] Szkudelski. The Mechanism of Alloxan and Streptozotocin Action in B Cells of the Rat Pancreas. Physiol Res. **2001**. 50: 536-546,

[6] Radhika B, Subash Vijayakumar, Ramaiyan Dhanpal. A Pharmacokinetic Interaction of Pioglitazone and Its Clinical Applications: A Short Review. Int. J. Pharm. **2012**, 2, 1-9

[7] Miyazaki, Y., M. Matsuda and R.A. DeFronzo. Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. Diabetes Care. **2002**. 25:517-523.

[8] Lindberg, M. and A. Astrup. The role of glitazones in management of type 2 diabetes. A dream or a nightmare. Obes. Rev. **2007**, 8: 381-384.