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Pharmacodynamic and Pharmacokinetic Drug Interaction Of Gliclazide and Olanzapine in Animal Models

Eswar Kumar K[1], Raghu Ram K[2], Swathi P[3], Jyotsna Rani P[4] and Gupta M.N[5]
[1,2,3,4,5] *(Pharmacology Division, A.U. College of Pharmaceutical Sciences,Andhra University, Andhra Pradesh, India)*

ABSTRACT
Studies were conducted in normal rats, alloxan induced diabetic rats and normal rabbits with oral administration of selected doses of gliclazide, olanzapine and their combination with adequate wash out periods in between treatments. Blood samples were collected from rats and rabbits at regular intervals of time and were analysed for glucose by GOD/POD method and for gliclazide by HPLC method. Glicazide produced hypoglycemia and antihyperglycemia in normal/diabetic rats with peak activity at 1h & 8h and 3h & 10 h respectively and in rabbits at 2 h. Therapeutic dose of olanzapine alone did not alter the normal blood glucose level and it did not alter the hypoglycemic response produced by gliclazide in combination. The same phenomenon observed in diabetic rats and rabbits also. There was no significant change in the serum levels and pharmacokinetic parameters of gliclazide when given in combination with olanzapine in normal rabbits. Hence it is concluded that single dose treatment with olanzapine has no influence on pharmacodynamics/ pharmacokinetics of gliclazide. Since the combination was found to be safe in two dissimilar species, the combination might be safe in humans also.

Keywords:-Drug interactions, Gliclazide, Olanzapine, Pharmacodynamics and Pharmacokinetics.

1. Introduction:
Now a days use of more than one drug (Polypharmacy) is a common practice to treat the chronic disorders like diabetes mellitus, hypertension etc. Polypharmacy is quite common practice all over the world to treat single disorder and multiple disorders which occur simultaneously. In such a situation one drug may interact with other drug leading to drug drug interactions. These interactions are more serious with high risk disorders like diabetes, hypertension or high risk drugs like antidiabetic, antihypertensive, antiarrhythmic drugs etc.

Diabetes mellitus is one such disorder which requires careful management of its therapy with respect to blood glucose levels. There are reports for the development of diabetes mellitus in patients with CNS disorders like depression and schizophrenia [1] [2]. In such situations there is every possibility for the use of multiple drug therapy i.e; anti diabetic drugs with drugs for the treatment of other associated disorders and these situations may lead to drug-drug interaction problems. Maintenance of normal blood glucose levels is essential in diabetes since a decrease in blood glucose levels (hypoglycemia) or increase in blood glucose levels (hyperglycemia) is unwanted phenomenon. Hence monitoring of anti diabetic drug therapy in presence of other drugs is very much needed in order to maintain the safety.

There are several reports that prevalence of type II diabetes in people with schizophrenia may be 2-4times higher than general population [3] and on chronic usage of atypical antipsychotic drugs may develop diabetes like conditions (hyperglycemia) [4] [5]. Oral hypoglycaemic agents are used in the treatment of type II diabetes, amongst which gliclazide, a second generation sulfonyl urea derivative is preferred in the therapy because of its selective inhibitory activity towards pancreatic K^+ATP channels, [6] [7] [8], antioxidant property, [9] [10] [11], low incidence of producing severe hypoglycaemia [12] [13] and other haemobiological effects [14] [15] [16]. Gliclazide induces the release of insulin by triggering calcium entry into the pancreatic β cells by blocking K^+ channels. Our earlier studies indicate interaction of gliclazide with several other classes of drugs [17] [18] [19] [20] [21]. Among atypical antipsychotic drugs olanzapine is most widely used to treat schizophrenia. The protein binding of gliclazide and olanzapine are 85-99% and 93% respectively and glucuronidation is one of the metabolic pathway involved in both the drugs [22] [23]. Since there is a possibility for their combined use in schizophrenia associated with diabetes mellitus and there is a chance of

interaction at distribution and metabolism it was planned to find out the safety of the combination in animal models. Hence in the present study the influence of olanzapine on the pharmacodynamics and pharmacokinetics of gliclazide was carried out in rats/rabbits.

2. Materials and Methods

Albino rats of either sex obtained from M/s. Mahaveer Enterprises, Hyderabad and albino rabbits of either sex obtained from M/s. Ghosh Enterprises, Kolkata were used in the study. All animals were maintained on pellet diet supplied by M/s. Rayan Biotechnologies Pvt. Ltd., Hyderabad with 12h/12h light/dark cycle and water *ad libitum*. Animals were fasted for 18 h before the experiment.

2.1 Study in normal rats:

A group of six albino rats weighing between 250-300 g were administered with 1mg/ kg body weight gliclazide, orally. The same group was administered with 0.9mg/ kg body weight olanzapine, orally after a wash out period of one week. The same group was also administered with 0.9mg/ kg body weight olanzapine 30 min prior to 1mg/ kg body weight gliclazide, after a further wash out period of 1 week. Blood samples were withdrawn from retro orbital puncture at 0,1,2,3,4,6,8,10 and 12h intervals. Blood samples were analysed for blood glucose levels by GOD/POD method [24] using commercial glucose kits (Span diagnostics).

2.2 Study in diabetic rats:

Diabetes was induced by the administration of alloxan monohydrate in two doses i.e.; 100 mg and 50mg/ kg body weight intraperitoneally for two consecutive days [25]. A group of 6 rats with blood glucose levels above 250 mg/dL was selected for the study. The study similar to the one conducted in normal rats was repeated in diabetic group.

2.3 Study in normal rabbits:

A group of six albino rabbits weighing between 1.38-1.7 kg were used in the study. They were administered with 5.6 mg/1.5 kg body weight gliclazide orally. The same group was administered with 0.7 mg/1.5 kg body weight olanzapine orally after a wash out period of 1 week. The same group was also administered with 0.7 mg/1.5 kg body weight olanzapine (single dose treatment) 30 min prior to 5.6 mg/1.5 kg body weight gliclazide after a further was out period of one week. Blood samples were collected at 0,1,2,3,4,6,8,12,16 and 24 h intervals by puncturing the marginal ear vein in all the experiments. Blood samples were analysed for blood glucose levels by GOD/POD method [24] using commercial glucose kits and for serum gliclazide concentration by HPLC method [26].
The animal experiments were approved by our Institutional Animal Ethics committee and by the Government regulatory body for animal research (Regd. No. 516/01/A/CPCSEA).

2.4 Data and Statistical analysis:

Data was expressed as Mean± Standard Error Mean (SEM). The significance was determined by applying students paired ‘t’ test.

3. Results

Gliclazide produced a biphasic response with peak hypoglycemic activities at 1 and 8 h in normal rats and at 3 and 10 h in diabetic rats, whereas it produced a single peak at 2 h in normal rabbits. Therapeutic dose of olanzapine alone did not alter the normal blood glucose level and it did not alter the hypoglycemic response produced by gliclazide in combination. The same phenomenon observed in diabetic rats also.

Single dose treatment of olanzapine given 30 min prior to gliclazide neither altered pharmacodynamic nor pharmacokinetic parameters of gliclazide in normal rabbits. There was no statistical significant interaction of gliclazide with olanzapine combination when compared to gliclazide control in the following parameters like K_a, t_{max}, C_{max}, AUC, AUMC, t1/2, MRT, Vd and clearance.

4. Discussion

Drug interactions are usually seen in clinical practice and the mechanisms of interactions are evaluated usually in animal models. We studied the influence of olanzapine on the pharmacodynamics of gliclazide in normal/diabetic rats and in normal rabbits and on the pharmacokinetics of gliclazide in normal rabbits. The normal rat model served to quickly identify the interaction. The diabetic rat model served to validate the same response in the actually used condition of the drug (in type II diabetes). The rabbit model is another dissimilar species to validate the occurrence of interaction in another species. It is well established that gliclazide acts by both pancreatic (Insulin release by K^+ channel inhibition in β cells) and extra pancreatic (tissue uptake of glucose) mechanisms. The target for sulfonylurea activity is ATP sensitive K^+ channels (K^+ATP channels). The sulfonylureas and related drugs used in type II diabetes stimulate insulin by closing K^+ATP channels in pancreatic β cells. The sulfonylureas target the SUR (sulfonylurea receptor) subunit of K^+ATP channels, which exists in several iso forms expressed in different tissues, SUR1 in pancreatic β cells, SUR2A in cardiac muscle and SUR2B in vascular smooth muscle [27]. The pancreatic cell ATP increases when plasma glucose level rises resulting in the closure of K^+ATP channels in plasma membrane, allows the cell to depolarize, triggering Ca^{+2} entry and insulin release [28].

Olanzapine is an atypical antipsychotic drug widely used for the treatment of schizophrenia. The dose of olanzapine is selected by human therapeutic dose extrapolated to rats basing on the body surface area. The gliclazide produced biphasic response in rat model may be due to its enterohepatic circulation in rats [29] [30] and in humans [31]. The selected dose of olanzapine produced a slight reduction in the blood glucose levels which was found to be insignificant. In combination it didn't alter the blood glucose reduction produced by gliclazide. Single dose treatment of olanzapine given 30 min prior to gliclazide did not alter the pharmacokinetic parameters of gliclazide in normal rabbits. There was no statistical significance of gliclazide with olanzapine combination when compared to gliclazide control in the following parameters like K_a, t_{max}, C_{max}, AUC, AUMC, $t_{1/2}$, MRT, Vd and clearance.

5. Figures and Tables

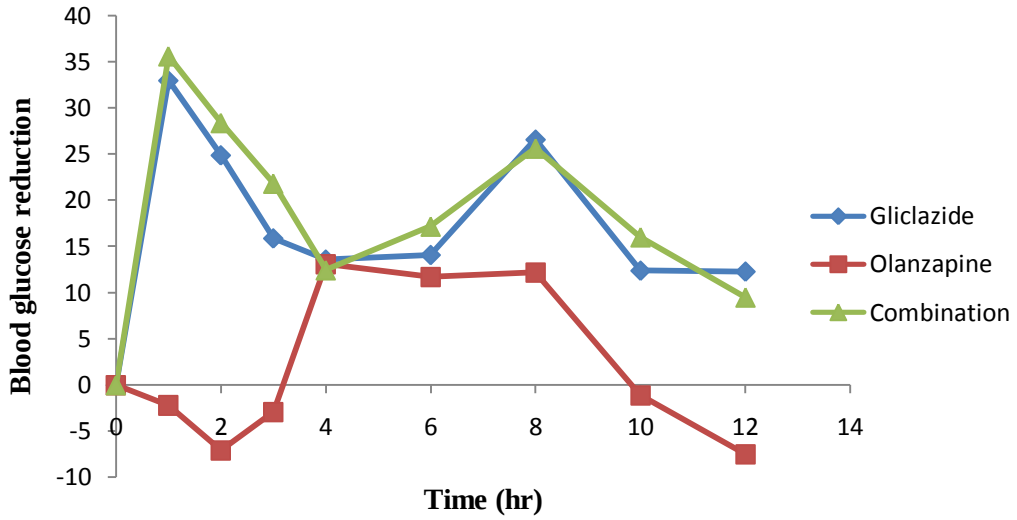

Fig 1: *Average percent blood glucose reduction after administration of gliclazide, olanzapine and their combination in normal rats (N=6)*

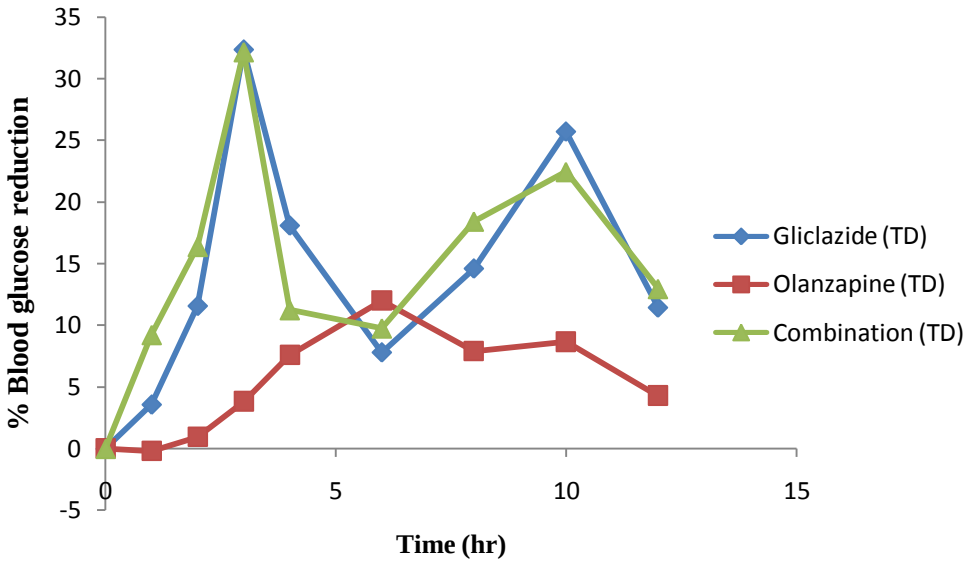

Fig 2: *Average percent blood glucose reduction after administration of gliclazide, olanzapine and their combination in diabetic rats (N=6)*

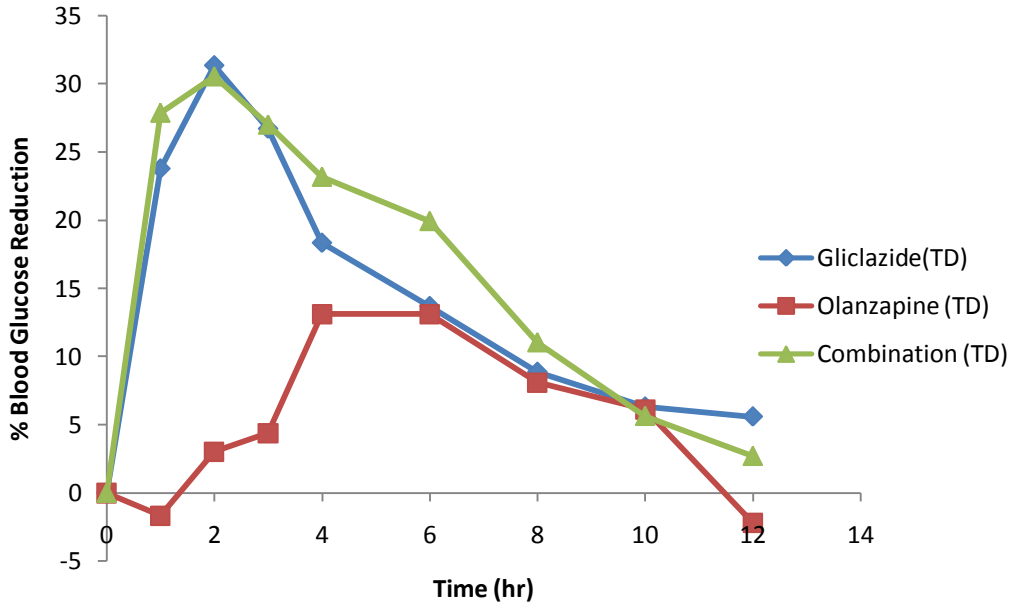

Fig 3: *Average percent blood glucose reduction after administration of gliclazide, olanzapine and their combination in normal rabbits (N=4)*

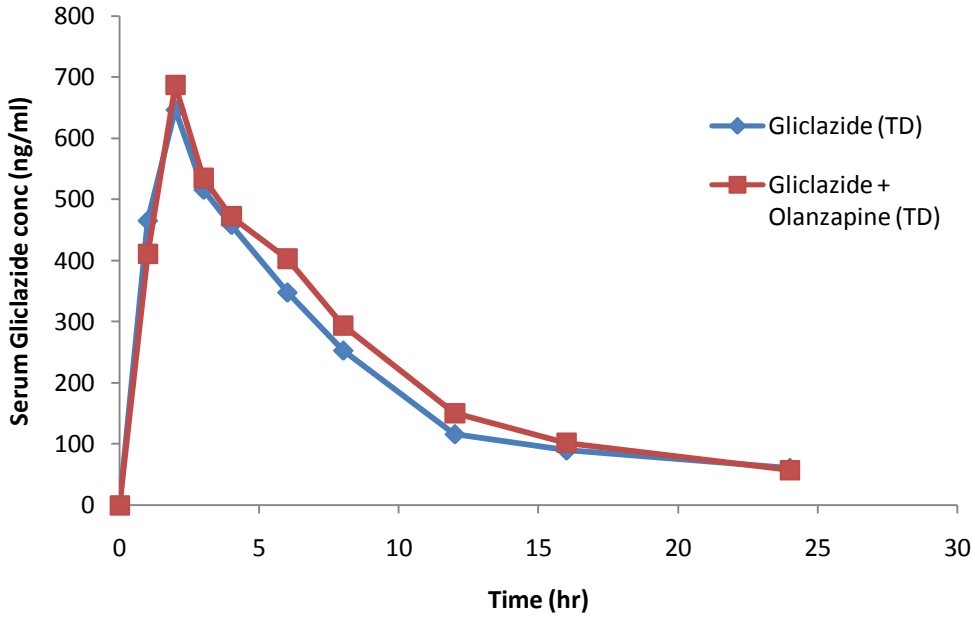

Fig 4: *Average serum gliclazide concentration (ng/ml) without and with Olanzapine treatment in normal rabbits (N=4)*

Table 1: Average percent blood glucose reduction after administration of gliclazide, olanzapine and their combination in normal/diabetic rats (N=6)

Time (h)	Normal rats			Diabetic rats		
	Gliclazide	Olanzapine	Gliclazide + Olanzapine	Gliclazide	Olanzapine	Gliclazide + Olanzapine
0	0	0	0	0	0	0
1	**33.0±2.8**	-2.20±0.98	**35.51±1.7**	3.58±1.68	-0.19±0.42	9.23±2.04
2	24.9±4.4	-7.10±1.34	28.40±3.2	11.58±3.41	1.88±1.6	16.38±1.92
3	15.9±6.0	-2.95±1.01	23.50±1.2	**32.36±4.55**	3.56±0.59	**32.17±0.66**
4	16.4±4.8	**13.11±2.77**	12.45±2.3	18.1±3.01	7.6±1.52	11.25±1.43
6	17.7±5.1	11.76±3.24	22.43±3.1	7.81±0.96	**12.0±0.91**	9.76±2.08
8	**26.6±4.8**	12.25±3.83	**25.58±3.1**	14.61±4.64	7.91±2.14	18.43±2.21
10	12.4±3.7	-1.18±2.63	16.05±2.6	**25.71±3.24**	8.66±2.08	**22.45±2.75**
12	12.3±3.7	-7.54±2.53	12.04±2.5	11.45±2.41	4.3±1.32	12.96±0.56

*Mean±SEM; *** Significant at P<0.001; ** Significant at P<0.01; * Significant at P<0.05 compared to gliclazide control*

Table 2: Average percent blood glucose reduction after administration of gliclazide, olanzapine and their combination in normal rabbits (N=4)

Time (h)	Gliclazide	Olanzapine	Gliclazide + Olanzapine
0	0	0	0
1	23.80±3.58	-1.65±1.03	27.950±0.42
2	**31.37±0.53**	4.30±1.60	**30.57±0.44**
3	26.72±1.48	4.37±1.71	27.02±2.70
4	18.35±3.54	**13.11±1.91**	23.20±3.11
6	13.70±2.77	13.10±1.74	19.95±2.86
8	8.87±2.64	8.10±1.49	11.05±1.49
10	6.32±2.46	6.11±2.11	5.65±0.74
12	5.60±2.09	-2.17±1.89	2.71±1.05

*Mean±SEM; *** Significant at P<0.001; ** Significant at P<0.01; * Significant at P<0.05 compared to gliclazide control*

Table 3: Average serum gliclazide concentration (ng/ml) without and with Olanzapine treatment in normal rabbits (N=4)

Time (h)	Gliclazide	Gliclazide +Olanzapine
0	0	0
1	465.62±44.19	410.50±26.63
2	646.87±34.58	686.87±4.84
3	516.25±29.46	534.87±4.85
4	458.75±23.57	472.50±5.52
6	348.12±25.66	403.0±9.04
8	253.12±31.95	294.12±2.12
12	116.25±18.41	150.87±4.42
16	89.68±9.92	102.0±2.80
24	61.00±12.17	57.12±1.0

*Mean±SEM; *** Significant at P<0.001; ** Significant at P<0.01; * Significant at P<0.05 compared to gliclazide control*

Table 4: Mean pharmacokinetic parameters of gliclazide before and after olanzapine administration in rabbits (N=4)

Pharmacokinetic parameter	Without Olanzapine	With Olanzapine
AUC_{0-24} (ng/ml/h)	5019.62±57.21	5313.38±135.96
$AUC_{0-\alpha}$ (ng/ml/h)	5614.29±166.14	5779.87±165.73
$AUMC_{0-24}$ (ng/ml/h*h)	37395.57±4171.14	36840.04±1249.82
$AUMC_{0-\alpha}$ (ng/ml/h*h)	57632.27±10822.18	52124.54±2260.53
K_e (h^{-1})	0.101±0.007	0.114±0.00
K_a (h^{-1})	2.30±0.0	2.3±0
$t_{1/2}$(h)	6.91±0.49	6.0525±0.07
V_{dss} (ml/kg)	6390.06±850.95	5588.1±119.02
Cl(ml/h/kg)	753.73±40.96	652.47±19.40
C_{max} (ng/ml)	646.87±34.58	2±0
T_{max}(h)	2.0±0.0	668±21.62
MRT (h)	10.14±1.58	9.00±0.15

*Mean±SEM; *** Significant at P<0.001; ** Significant at P<0.01; * Significant at P<0.05 compared to gliclazide control*

6. Conclusion

When pharmcodynamics response was considered, single dose treatment of olanzapine did not alter the hypoglycemic response produced by gliclazide in rabbits and rats. Since olanzapine has not altered gliclazide response it appears that olanzapine has no influence on the pancreatic and extra pancreatic (cellular utilization of glucose) mechanisms that influence blood glucose. There was no significant change in pharmacokinetic parameters of gliclazide in presence of olanzapine in normal rabbits. Hence it is concluded that single dose treatment with olanzapine has no influence on pharmacodynamics/ pharmacokinetics of gliclazide. Since the combination was found to be safe in two dissimilar species, the combination was assumed to be safe in humans also.

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