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Research Article

PHARMACODYNAMIC AND PHARMACOKINETIC DRUG INTERACTION OF GLICLAZIDE AND RISPERIDONE IN ANIMAL MODELS

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ABSTRACT

The study was conducted to find out the influence of risperidone on the pharmacodynamics and pharmacokinetics of gliclazide, which is widely used drug for type II diabetes. Studies were conducted in normal rats; alloxan induced diabetic rats and normal rabbits with oral administration of selected doses of gliclazide, risperidone and their combination with adequate wash out periods in between treatments. Blood samples were collected from rats/rabbits by retro orbital/marginal ear vein puncture respectively at regular intervals of time. All the blood samples were analyzed for glucose by GOD/POD method and for gliclazide by HPLC. Gliclazide produced significant hypoglycemia and antihyperglycemia response in normal/diabetic rats and in rabbits. Therapeutic dose of risperidone alone did not alter the normal blood glucose level and the hypoglycemic response produced by gliclazide in combination in normal rats. Similar phenomenon was observed both in diabetic and normal rabbits. There was a significant change in the pharmacokinetic parameters of gliclazide like, AUMC, $t_{1/2}$, K_e, V_{dss} clearance and MRT when given in combination with risperidone in normal rabbits, indicating the change in elimination pattern of gliclazide in the presence of risperidone**.** This might be due to the increase in the pH of urine by risperidone which might be facilitated the elimination of gliclazide, a weakly acidic drug in later hours. The single dose treatment did not produce the change in the hypoglycemic activity, but multiple dose treatment may reduce the gliclazide activity. Hence the therapy with the combination needs adjustment of dosing intervals between the treatments.

Keywords: Drug interactions, Gliclazide**,** Risperidone, Pharmacodynamics, Pharmacokinetics

INTRODUCTION

Now a day's use of more than one drug (polypharmacy) or using herbal medications along with the prescribed medication is a common practice to treat the chronic disorders like diabetes mellitus, hypertension etc which may lead to many interactions[1]. 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 [2,3]. 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 antidiabetic 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 2-4 times higher than general population [4] and on chronic usage of atypical antipsychotic drugs may develop diabetes like conditions (hyperglycemia) [5,6]. Oral hypoglycemic agents are used in the treatment of type II diabetes, amongst which gliclazide, a second generation sulfonylurea derivative is preferred in the therapy because of its selective inhibitory activity towards pancreatic K^+ATP channels,[7,8,9], antioxidant property,[10,11,12], low incidence of producing severe hypoglycemia[13,14] and other haemobiological effects [15,16,17]. Gliclazide induces the release of insulin by triggering calcium entry into the pancreatic β cells by blocking K^+ channels**.** Earlier studies indicate interaction of gliclazide and many other antidiabetic drugs with several other classes of drugs[18,19,20,21,22,23]. Among atypical antipsychotic drugs risperidone is most widely used to treat schizophrenia. The protein binding of gliclazide and risperidone are 85-99% and 90% respectively and both the drugs are metabolized to a certain level by CYP 3A4 enzyme[24,25,26]. 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 risperidone on the pharmacodynamics and pharmacokinetics of gliclazide was carried out in rats/rabbits.

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.

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 0.54mg/ kg body weight risperidone, orally after a wash out period of one week. The same group was also administered with 0.54mg/ kg body weight risperidone 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, 4, 8, 12, 16, 20 and 24h intervals. Blood samples were analyzed for blood glucose levels by GOD/POD method [27] using commercial glucose kits (Span diagnostics).

Study in diabetic rats

Diabetes was induced by the administration of alloxan monohydrate in two doses 100 mg and 50mg/ kg body weight intraperitoneally for two consecutive days [28]. 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.

Study in normal rabbits

A group of four 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 0.45 mg/1.5 kg body weight risperidone given orally after a wash out period of 1 week. The same group was also administered with 0.45 mg/1.5 kg body weight risperidone (single dose treatment) 30 min prior to 5.6 mg/1.5 kg body weight gliclazide was administered. Blood samples were collected at 0, 4, 8, 16, 20 and 24 h intervals by puncturing the marginal ear vein in all experiments. Blood samples were analyzed for blood glucose levels by GOD/POD method [27] using commercial glucose kits and for serum gliclazide concentration by HPLC method [29]. 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).

Data and Statistical analysis

Data were expressed as mean ± standard error of mean (SEM). The significance was determined by applying student`s paired 't' test.

RESULTS

When blood samples withdrawn at 4 h interval up to 24h were analyzed, gliclazide produced peak hypoglycemic activity at 4 h in normal and diabetic rats and in normal rabbits. Therapeutic dose of risperidone 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.

Table 1: Mean percent blood glucose reduction before and after treatment with risperidone in normal rats (N=6).

Mean percent blood glucose reduction (Mean±SEM)			
Time(hr)	**Gliclazide**	**Risperidone**	**Combination**
0	0	0	0
4	10.25±1.63	-2.07±2.59	14.81±2.26
8	23.18±2.11	2.0±4.89	21.83±3.26
12	11.20±2.08	6.53±2.71	17.71±4.88
16	-0.86±2.35	10.23±2.44	0.95±3.19
20	-5.09±2.19	7.36±1.72	6.63±2.51
24	-5.52±1.68	12.35±2.82	2.71±3.16

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

Table 2: Mean percent blood glucose reduction before and after treatment with risperidone in Diabetic rats (N=6)

Mean percent blood glucose reduction (Mean±SEM)			
Time(hr)	**Gliclazide**	**Risperidone**	**Combination**
0	0	0	0
4	17.48±3.05	1.35±2.71	12.26±1.82
8	14.61±4.66	5.76±1.35	17.83±1.80
12	16.46±2.20	11.78±0.80	13.71±0.98
16	7.73±0.39	11.1±1.77	7.76±0.62
20	0.8±0.25	6.42±1.47	3.88±1.05
24	-1.2±0.09	-2.26±2.41	2.07±1.76

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

Single dose treatment of risperidone given 30 min prior to gliclazide did not alter pharmacodynamic parameters of gliclazide in normal rabbits. In the pharmacokinetic parameters, there was no change in absorption parameters of gliclazide like AUC, K_a, C_{max}, t_{max} and Cl but, there was a significant change in the elimination parameters of gliclazide like Ke, $t_{1/2}$, Vd, AUMC and MRT in the presence of risperidone in normal rabbits. This indicates that there is no change in the pattern of absorption and availability of gliclazide however; there was a change in the pattern of elimination of gliclazide in the presence of risperidone which is not affecting the pharmacodynamic effect of gliclazide.

Table 3: Mean percent blood glucose reduction before and after treatment with risperidone in normal rabbits (N=4)

Percent blood glucose reduction (Mean±SEM)			
Time(hr)	**Gliclazide**	**Risperidone**	**Combination**
0	0	0	0
4	18.35±3.54	-4.52±1.87	12.84±3.23
8	8.87±2.64	5.52±3.94	5.84±4.34
12	5.07±2.57	12.67±1.04	2.88±1.13
16	-1.7±0.64	4.7±1.97	4.7±1.97
20	-3.6±0.70	0.43±1.36	-6.1±3.59
24	-4.62±1.19	0.68±0.75	-7.825±2.46

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

Table 4: Mean serum gliclazide levels before and after treatment with risperidone in normal rabbits (N=4)

Serum gliclazide concentration in ng/ml (MEAN±SEM)		
Time(hr)	**Gliclazide**	**Risperidone+Gliclazide**
0	0	0
4	458.75±42.14	487.5 ±50
8	253.12±63.91	259.37±43.75
12	116.25±36.8	99.37±31.97
16	89.63±19.85	68.75±17.5
20	68.97±12.49	41.25±14.50
24	52.42±7.25	20±11.90

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

Table 5: Mean pharmacokinetic parameter of gliclazide before and after Risperidone administration in rabbits (N=4)

Parameter	Gliclazide	Gliclazide+Risperidone	Significance at p<0.05
AUC(0-24) (ng/ml)*h	4052±40.7	3865±244.64	Not significant
AUC(0-α) (ng/ml)*h	5038.53±222.96	4032.23±303.83	Not significant
AUMC(0-24) (ng/ml)*h*h	35093.74±1727.3	17473.46±3637.93	*Significant
AUMC(0-α) (ng/ml)*h*h	80859.28±15698	22940.57±5818.4	Not significant
Ke (per hr)	0.06±0.014	0.13±0.02	*Significant
Ka (per hr)	1.15±0	1.15±0	Not significant
$T_{1/2}$ (hr)	12.95±3.38	5.33±0.77	*Significant
Vdss (ml/hr)	12018.45±1831.6	4255.1±644.77	*Significant
Cl (ml/hr)	782.1±22.9	945.3±64.18	Not significant
Tmax (hr)	4±0	4±0	Not significant
Cmax (ng/ml)	458.62±23.56	487.5±25	Not significant
MRT(hr)	15.73±2.34	5.69±1.13	*Significant

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

DISCUSSION

Drug interactions are usually seen in clinical practice and the mechanisms of interaction are evaluated usually in animal models. We studied the influence of risperidone on the pharmacodynamics of gliclazide in normal and diabetic rats and also in normal rabbits. Additonally pharmacokinetics of gliclazlide was studied in normal rabbits. The normal 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 species. It is well established that gliclazide acts by both pancreatic (Insulin release by K^+ channel inhibition the β cells) and extra pancreatic (tissue uptake of glucose) mechanism. The target for sulphonylureas activity is ATP sensitive K^+ channels (K^+ATP channels). The sulphonylureas and related drugs used in type II diabetes stimulate insulin release by closing K^+ATP channels in pancreatic β cells. The sulphonylureas target the SUR (sulphonylurea receptor) subunit of K^+ATP channels, which exists in several isoforms expressed in different tissues, SUR1 in pancreatic β cells, SUR2A in cardiac muscle and SUR2B in vascular smooth muscle[30]. The pancreatic β cell ATP increases when plasma glucose level rises resulting in the closure of K^+ ATP channels in plasma membrane, allows the cells to depolarize, triggering Ca^{2+}entry and insulin release [31].

Risperidone is an atypical antipsychotic drug widely used for the treatment of schizophrenia. The dose of risperidone is selected by human therapeutic dose extrapolated to rats basing on the body surface area. Single dose treatment of risperidone alone and in combination with gliclazide did not alter the blood glucose level in normal rats indicating the absence of interaction. The same pattern was observed in alloxan induced diabetic rats. The results in normal and diabetic rats indicate absence of interaction in rats (rodent species). Risperidone did not alter the hypoglycemic effect of gliclazide in normal rabbits indicating that non existence of interaction between risperidone and gliclazide in non rodent species also. In the pharmacokinetic parameters there was no change in absorption parameters of gliclazide but there was significant change in the elimination parameters like Ke, $T_{1/2}$, Vd, AUMC and MRT in the presence of risperidone in normal rabbits. There was no significant alteration in AUC, K_a, C_{max}, T_{max} and Cl. It indicates there is no change in the pattern of absorption and availability of gliclazide in the presence of risperidone. There was significant change was found in Ke, $T_{1/2}$, Vd AUMC and MRT of gliclazide in risperidone treatment group indicating there was a change in the pattern of elimination of gliclazide in the presence of risperidone. This may be due to the increase in the urinary pH in the presence of risperidone**,** being a basic drug in later hours which might facilitate the elimination of Gliclazide, a weakly acidic drug in the later hours. The change in the elimination pattern of gliclazide did not result in much severe hypoglycemia; hence the combination may be safe with acute treatment. The combination may produce more severe interaction with multiple dose treatments, which may reduce the efficacy of gliclazide therapy.

CONCLUSIONS

Since the combination of acute treatment of risperidone and gliclazide did not result in interaction in two dissimilar species, the combination may be safe in humans with acute treatment. However, the combination resulting in the change in the elimination pattern of gliclazide in the later hours, the multiple dose treatment may result in much severe hypoglycaemia. Hence the therapy with the combination needs to be monitored in clinical practice.

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