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INFLUENCE OF *TAMARINDUS INDICA* ON PHARMACODYNAMICS AND PHARMACOKINETICS OF *GLICLAZIDE* IN RATS / RABBITS

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ABSTRACT

The study was conducted in rats and rabbits with selected oral doses of gliclazide, *Tamarindus indica* and their combination to evaluate the safety of gliclazide therapy in the presence of *Tamarindus indica*. Blood samples were collected from rats/rabbits by retro orbital/marginal ear vein puncture respectively at regular intervals of time. The blood glucose was estimated by GOD/POD method and serum gliclazide levels by HPLC method. *Tamarindus indica* alone reduced blood glucose levels in rats/rabbits and has slightly altered the hypoglycaemic effect of gliclazide when administered together. The serum gliclazide levels were reduced significantly and pharmacokinetic parameters of gliclazide were altered significantly in presence of *Tamarindus indica*, but did not result in the significant change in blood glucose levels, indicating that the reduction in the absorption of *Tamarindus* itself along with absorption of gliclazide. The decrease in the pharmacokinetic parameters like AUC, Cmax, Ka, Cl and increase in the $T_{1/2}$ indicate the decrease in the absorption and elimination of gliclazide, which might be due to laxative property of *Tamarindus*. In conclusion, the combination might not be safe with respect to its hypoglycaemic effect, but care should be taken when gliclazide is administered with multiple doses of *Tamarindus indica* in a clinical situation.

KEYWORDS: Gliclazide, *Tamarindus indica*, Blood Glucose.

INTRODUCTION

Along with the antidiabetic drugs, diet also plays a major role in the treatment of Type-II diabetes. Many dietary substances have medicinal properties and are used in traditional medicine to treat various ailments. Substances such as garlic[1], cinnamon[2], bitter gourd[3], ginger[4] and many such dietary sources, which had antidiabetic properties. When these used along with the antidiabetic drugs might lead to interactions and may alter the activity of the drug.

Due to an increased demand of herbal drug usage and concomitant administration may lead to interactions between herbs and allopathic drugs. Certain herbal supplements can cause potentially dangerous side effects when taken with prescription drugs. Among such herbs *Tamarindus indica* is widely used in Indian cuisine daily and is used in Indian Ayurvedic medicine for gastric and/or digestion problems, and in cardioprotective activity. *Tamarindus indica* Linn (family: Caesalpiniaceae) is known as tamarind, a well known plant of the Indian medicinal system. The fruit pulp has been reported to contain ascorbic acid, β-carotene, tartaric acid, lactic acid, citric acid, and maleic acid which are responsible for hepatoprotective activity. Some pulp of fruits has antidiabetic, hypolipidemic, antioxidant and hepatoregenerative activities.[5,6]

Experimental studies have shown that herb-drug interactions have both a pharmacokinetic and pharmacodynamic basis, most of that are attributed to the induction or inhibition of hepatic and intestinal microsomal enzymes (primarily cytochrome P450) drug transporters.[7]

Hence the present study is planned to evaluate the influence of *Tamarindus indica* pulp on pharmacodynamic and pharmacokinetic properties of selected antidiabetic drug Gliclazide.

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 100mg/ kg body weight *Tamarindus indica*, orally after a wash out period of one week. The same group was also administered with 100mg/ kg body weight *Tamarindus indica* 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[8] 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.[9] 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 150 mg/1.5 kg body weight *Tamarindus indica* given orally after a wash out period of 1 week. The same group was also administered with 150 mg/1.5 kg body weight *Tamarindus indica* (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 using commercial glucose kits and for serum gliclazide concentration by HPLC method. 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).

RESULTS AND DISCUSSION

Diabetes mellitus is one such disorder where polypharmacy is used as it is generally associated with many complications. Type-II diabetes is more common than type - I diabetes.[10] Sulphonylureas are the drugs of choice in the treatment of type- II diabetes.[11] Among them gliclazide is widely used drug because of its high potency, prolonged action and lower incidence of side effects[12] and antioxidant activity.[13] The predominant effect of sulfonylureas is on the insulin secretion.[14] Sulphonylureas also stimulate the release of somatostatin, and they may suppress the secretion of glucagon slightly.[15]

In diabetic condition, maintenance of optimal level of blood glucose is essential since hyperglycaemia and hypoglycaemia are unwanted phenomenon. This is obtained by the use of antidiabetic drugs, proper diet and exercise.[16] The herb *Tamarind* is used in Indian system of medicine for various G.I complications and its Tamarind is reported to have effect in altering the cholesterol and blood glucose levels in animal studies.[17] The same has been consumed by the people as a dietary source daily and it may have influence on blood glucose levels and it may interfere with antidiabetic therapy in diabetics. Hence there is need for safety evaluation of antidiabetic therapy in presence of *Tamarind* with respect to optimal blood glucose maintenance.

The present study was planned to find out the influence of *Tamarindus indica* on pharmacodynamics of gliclazide in rats (rodent) and pharmacodynamics as well as pharmacokinetics of gliclazide in rabbits (non rodent). Since rat and rabbit are two dissimilar species, if the interaction occurs in both the species, then there is more probability of its occurrence in humans also. Similarly if absence of interaction is seen in both species, it is assumed to be absent in humans also.

The normal rats were selected for preliminary and quick screening of the drugs and small volumes of blood were collected at regular time intervals for the estimation of blood glucose levels. Dose dependent relationship was observed with 0.5mg/kg, 1 mg/Kg, and 2mg/Kg body weight of gliclazide in normal rats. From these three doses 1 mg/Kg of gliclazide was selected for interaction study as it produced optimum blood glucose reduction which is about 30-40% (table 1). A dose of 1mg/kg body weight of gliclazide produced a biphasic reduction in blood glucose levels. The biphasic response may be due to the entero-hepatic cycling in normal rats.[18] The effect of gliclazide on blood glucose levels was studied in the absence and presence of the interacting herb. In normal rats 100mg/kg body weight of *Tamarindus indica* produced hypoglycemic activity with peak activity at 6h and slightly increased the hypoglycemic effect of gliclazide when administered in combination.

Based on the results obtained from the normal rats, the study was extended to alloxan induced diabetic rats to find out the drug interaction in diabetic condition. In diabetic rats 100mg/kg body weight of *Tamarindus indica* produced antihyperglycemic activity which might be due to its inhibitory activity on the absorption of carbohydrates. This lowers the blood glucose levels of diabetic patients after meals.[19] Tamarind juice prevents oxidative damage in the pancreas which is linked with diabetes. In combination the *Tamarindus indica* decreased the hypoglycemic effect of gliclazide in 3h and 6h (table 2). This may be due to the decreased absorption of gliclazide due to increased motility of the G.I.T. So there is not much significant pharmacodynamic interaction between the *Tamarindus indica* and gliclazide in diabetic condition.

Later the study was conducted in rabbits also to find out the exact mechanism of the interaction to find whether

both pharmacokinetics and / or pharmacodynamics are involved in the interaction if it exists. A dose of 5.6mg/kg body weight of gliclazide produced hypoglycemic activity with peak effect at 2h in normal rabbits. The serum gliclazide levels were found to be high at 2h. That shows blood glucose levels were correlating with serum gliclazide levels. *Tamarindus indica* produced a slight hypoglycemic activity with peak effect at 3h and 8h in normal rabbits (table 3). In combination the *Tamarindus indica* decreased the hypoglycemic effect of gliclazide in normal rabbits which may be due to the decreased absorption of gliclazide due to increased motility.

The serum gliclazide levels were found to be suppressed in the presence of *Tamarindus indica* and there is a change in the peak activity of gliclazide (table 4). The pharmacokinetic parameters like AUMC, $T_{1/2}$, V_{dss} and MRT were significantly enhanced in the presence of Tamarind pulp. This indicates the change in the absorption and distribution of gliclazide (table 5). The absorption of gliclazide seems to be inhibited in the presence of Tamarind pulp. As per earlier reports on *Tamarindus indica* is said to increase the motility of the gastrointestinal tract which in turn decreases the absorption of the gliclazide in normal rabbits.[20] The increase in Vd might be due to presence of salt in its pulp as preservative. The decrease in the elimination of gliclazide might be due to decreased serum levels, resulted from decreased absorption and increased distribution. The decrease in the serum levels of gliclazide did not result in decreased activity of gliclazide, since *Tamarindus indica* itself found to produce hypoglycaemia.

Table 1: Mean Percent blood glucose reduction of *Tamarindus indica*, Gliclazide and in combination in normal rats.

Time (hrs)	Gliclazide (1mg/kg)	*Tamarindus indica* (100mg/kg)	Combination
0	00.00	00.00	00.00^{ns}
1	**33.0±2.82**	07.85±08.41	**33.18±06.37** ^{ns}
2	24.9±4.44	4.36±10.58	33.48±17.43 ^{ns}
3	15.9±6.06	13.25±06.66	26.8±15.55*
4	13.6±4.82	11.91±05.37	17.45±11.29*
6	14.7±5.14	**27.90±18.24**	**34.68±08.43*****
8	**26.6±4.83**	19.46±14.93	34.16±08.99***
10	12.4±3.70	18.73±09.90	27.11±07.17**
12	12.3±3.71	09.84±08.92	22.81±06.42**

nsP>0.05,* P<0.05,** P<0.01,***P<0.001 significance followed by two way ANOVA, Bonferroni's post test compared with gliclazide.

Table 2: Mean Percent blood glucose reduction of *Tamarindus indica*, Gliclazide and in combination in diabetic rats.

Time (hrs)	Gliclazide (1mg/kg)	*Tamarindus indica* (100mg/kg)	Combination
0	00.00	00.00	00.00 ^{ns}
1	03.28±1.78	07.21±7.06	00.99±1.77*
2	11.58±3.41	10.51±5.22	04.65±1.79**
3	**32.36±4.55**	**18.11±5.95**	**12.23±2.88*****
4	14.93±4.23	17.01±5.94	08.88±3.61*
6	04.41±1.51	**24.16±3.18**	**16.76±5.67****
8	07.63±6.15	19.91±5.31	12.98±5.47*
10	**25.71±3.24**	17.93±1.72	09.03±4.81***
12	11.45±2.41	14.71±1.96	05.19±3.03**

nsP>0.05,* P<0.05,** P<0.01,***P<0.001 significance followed by two way ANOVA, Bonferroni's post testcompared with gliclazide.

Table 3: Mean Percent blood glucose reduction of *Tamarindus indica*, Gliclazide and in combination in normal rabbits.

Time (hrs)	Gliclazide (5.6mg/1.5kg)	*Tamarindus indica* (150mg/1.5kg)	Combination
0	00.00	00.00	00.00^{ns}
1	23.80±3.58	08.57±09.04	19.77±13.57*
2	**31.37±0.53**	14.74±04.75	18.94±12.55**
3	26.72±1.48	**18.67±04.96**	**23.89±07.49** ^{ns}
4	18.35±3.54	17.95±10.67	19.70±19.31 ^{ns}
6	13.70±2.77	15.15±07.32	18.64±13.57 ^{ns}
8	08.87±2.64	13.02±13.86	16.90±08.27*
10	06.32±2.46	12.88±06.08	15.42±21.58**
12	05.60±2.09	10.01±03.81	14.07±15.98***

nsP>0.05,* P<0.05,** P<0.01,***P<0.001 significance followed by two way ANOVA, Bonferroni's post testcompared with gliclazide.

Table 4: Pharmacokinetics of Gliclazide and in combination with *Tamarindus indica* in normal rabbits.

Time (hrs)	Gliclazide (5.6mg/1.5kg)	Gliclazide+ *Tamarindus indica*
1	465.62±44.19	182.1±14.94***
2	**646.87±34.58**	**273.64±24.6*****
3	516.25±29.46	291.7±37.26**
4	458.75±23.57	226.1±33.65*
6	348.12±25.66	292.3±41.52*
8	253.12±31.95	217.3±27.13*
12	116.25±18.41	179.1±18.19*
16	89.68±9.92	134.8±19.20*
24	61.00±12.17	114.2±30.89*

nsP>0.05,* P<0.05,** P<0.01,***P<0.001 significance followed by two way ANOVA, Bonferroni's post testcompared with gliclazide

Table 5: Mean pharmacokinetic parameter of gliclazide before and after *Tamarindus indica* administration in rabbits (N=4).

Pharmacokinetic parameters	Gliclazide	Gliclazide+ *Tamarindus indica*
$AUC_{(0-24)}$	5019.62±57.21	4306.31±1099.12 ^{ns}
$AUC_{(0-\alpha)}$	5614.29±166.14	7892.13±1262.04*
$AUMC_{(0-24)}$	37395.57±4171.14	63219.91±19709.76*
$AUMC_{(0-\alpha)}$	57632.27±10822.18	285202.8±122580.5*
K_e	0.0659±0.01499	0.0363±0.0190**
K_a	2.31±0.2	0.864±0.191***
$t_{1/2}$	6.91±0.49	23.3±11.72 ^{ns}
V_{dss}	7164.56±804.58	17192.48±5642.12 ^{ns}
Cl	753.73±40.96	515.4612±75.39*
t_{max}	2.0±0.0	5.5±1**
C_{max}	646.87±34.58	358±99.1*
MRT	10.14±1.58	35.6±13.6*

^{ns} P>0.05,**P<0.01,***P<0.001, Significance followed by Two way ANOVA followed by Bonferonni's post test compared with Gliclazide.

CONCLUSIONS

Since there was an interaction in two dissimilar species (rats/rabbits), the combination might not be safe in humans also. Health care professionals should caution diabetic patients when such combination is prescribed. Serum glucose levels may need to be monitored by a healthcare provider, and medication adjustments may be necessary.

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