Research Paper

Interactions of Pearl Millet Diet on Pharmacodynamics and Pharmacokinetics of Gliclazide in Healthy Rats

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Pearl millet helps keep blood sugar levels stable for the long term in patients with diabetes because it has a relatively low glycemic index. The objective of this study was to determine the potential pharmacokinetics of food-drug interactions between 30 % and 60 % pearl millet diet and gliclazide in normal rats. Reduction of blood glucose by gliclazide (1 mg/kg) and pearl millet diet 30 and 60 was evaluated and it was observed that 30.9 % after 2 h and 19.53 % after 6 h reduction with gliclazide and pearl millet diet 60 showed 29.74 % after 3 h. Single and repeated dose studies are conducted and the gliclazide+pearl millet diet 60-repeated dose study showed a significant increase in percentage blood glucose reduction compared to single-dose study. Serum gliclazide levels are also observed in respective to blood glucose levels. However, there was no reduction in hemoglobin A1c and no increase in insulin with gliclazide+pearl millet diet 60-repeated dose. The pharmacokinetic parameters of gliclazide were estimated in correlation between concentration and sampling time using the PKSolver program. The pharmacokinetic analysis explained the changes in elimination half-life, time to peak drug concentration, maximum plasma concentration and mean residence time corresponding to the serum levels of gliclazide in gliclazide+pearl millet diet 60-repeated dose. Interactions may be due to the inhibition of cytochrome P450 3A4 by millet leading to increased concentrations of gliclazide and subsequently increased glucose reduction. To avoid potential hypoglycemia, physicians should be aware of these interactions and adjust the dosage of gliclazide accordingly.

Key words: Pearl millet, gliclazide, pharmacodynamics, pharmacokinetics, blood glucose

Management of diabetes and its associated complications can be economically achieved through dietary management[1]. Several diabetes associations around the world provide dietary guidelines for carbohydrates, protein, fat, fiber and sodium to promote healthy eating habits in individuals with diabetes. American Diabetes Association (ADA) states that carbohydrates should make up 45 %-60 % of total caloric intake, protein 15 %-20 % and fat 25 %-35 %[2]. It is also recommended to consume at least 14 g of fiber per 1000 calories and limit sodium intake to less than 2300 mg/d. Canadian Diabetes Association recommends a similar distribution of macronutrients with a daily fiber intake of 25-50 g[3]. UK Diabetes Guidelines are close to the ADA recommendations, but suggest a slightly lower fat intake of 30 % or less of total calories. European Association for the Study of Diabetes also promotes similar guidelines for carbohydrate, protein and fat intake, emphasizing a daily fiber intake of at least 25 g while limiting sodium intake to 2000 to 2400 mg/d[4]. Gliclazide is a second-generation sulfonylurea and the second most commonly prescribed oral antihyperglycemic agent for Type 2 Diabetes Mellitus (T2DM) after metformin[5]. It is preferred because it selectively binds to the pancreatic β-cell Sulfonylurea Receptor (SUR1) and stimulates insulin release. It also has unique antioxidant properties and other beneficial effects on blood components. In addition, gliclazide restores peripheral insulin sensitivity, reduces hepatic glucose production and reduces skeletal muscle glycogenesis, which is unrelated to its insulin-mediated effects[6]. Due to its extrapancreatic action, gliclazide may have

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potential for the treatment of Type 1 Diabetes Mellitus (T1DM), especially in combination with other substances that have hypoglycemic effects, such as some bile acids and probiotics[7].

It is a lifestyle-related disorder and can be prevented and controlled through dietary changes along with prescribed medications. The most beneficial are low Glycemic Index (GI), high fiber content, Polyunsaturated Fatty Acids (PUFA), non-acid-forming potential and gluten-free. Millets are nutrients rich in vitamins, minerals, proteins, essential fatty acids, energy, carbohydrates, plant chemicals and non-glycemic polysaccharides[8]. Polyphenols present in the layer of millet seeds enrich them with antioxidant and antidiabetic properties. These polyphenols interact with CYP450 enzymes, leading to either induction or inhibition of CYP, which alters the pharmacokinetic parameters of their respective substrate drugs[9]. The proposed gliclazide is extensively metabolized in the liver to inactive metabolites by CYP-mediated metabolism[10].

The primary objective of this research was to investigate the correlation between millet consumption and blood glucose levels. The main goal was to create scientific evidence to support the claim that millet can lower blood glucose levels. In addition, the study aimed to investigate the integration of pearl millet into a regular diet and to assess its effectiveness in achieving a substantial 30 %-40 % reduction in blood glucose levels in rats. The focus was to determine the dose-response relationship between these types of millets and blood glucose levels in normal rats. The intention was to identify the optimal dosage required to achieve a targeted percentage reduction in blood glucose levels, thereby contributing to valuable knowledge about the potential health benefits of incorporating millet into dietary practices.

MATERIALS AND METHODS

In this research phase, a uniform set of experimental conditions and protocols was employed for all selected drugs, encompassing various millet diet ratios as well as the reference drug, gliclazide. Albino rats of the Wistar strain, obtained from Mahaveer Enterprises, Hyderabad, India, and of either gender were utilized as subjects for the study. The animals were housed in standard laboratory conditions, maintaining an ambient temperature of 25±2° and a relative humidity of 50±15 %, with a 12 h light/12 h dark cycle. The rats were provided with a commercial pellet diet from Rayan's Biotechnologies Pvt. Ltd., Hyderabad, India and had access to water *ad libitum*. Ethical considerations were paramount, as the experimental protocol underwent rigorous scrutiny and approval by both the Institutional Animal Ethics Committee and the regulatory body of the government (Regd No.SNV/08/2022/PC/1).

To ensure uniformity and compliance with ethical standards, the rats underwent a fasting period of 18 h before the commencement of the experiment, during which they had access to water. Subsequently, both food and water were withdrawn for the duration of the experiment. The focus of this particular segment of the study was to exclusively assess the pharmacodynamic response, with a specific emphasis on blood glucose and insulin levels. As a benchmark for comparison, gliclazide was chosen as the standard reference drug. This comprehensive experimental framework laid the foundation for a meticulous examination of the effects of various millet diet ratios and gliclazide compared to the established interaction type, contributing to a nuanced understanding of their pharmacodynamic properties and pharmacokinetic interactions.

Preparation of drug solutions:

Millet preparation: Dried forms of millet were collected from the local market and fine powders of the obtained pearl millet and sieved to fine powder. The millets are mixed with the basal diet at a ratio of 30 % and 60 % with pearl millet.

Gliclazide stock solution (10 mg/ml): The stock solution is prepared by adding a few drops of 0.1 N NaOH to solubilize gliclazide and adjusting the volume with distilled water. Appropriate dilutions were made with distilled water as and when needed.

Experimental design:

Normal Albino rats of either gender weighing between 220-270 g were used in the study. The animals were fasted overnight for 18 h before experimentation but allowed free access to water. Water was withdrawn during the experiment. Fasted rats were divided into four groups with six animals in each group and treated orally in the following manner. The experimental design in

normal rats was conducted into 4 stages and each stage is separated by a washout period of 7 d.

Stage I: Rats were administered with vehicle control (water) and standard (Gliclazide 1.0 mg/kg body weight (b. wt)) and blood samples were collected at different time intervals and were analyzed for blood glucose.

Stage II: Different groups of rats were fed with interacting pearl millet and blood samples were collected at different time intervals and were analyzed for blood glucose.

Stage III: Rats were fed with pearl millet and along with the gliclazide 1 mg/kg b. wt was administered and blood samples were collected at different time intervals and were analyzed for blood glucose.

Stage IV: Rats were fed with multiple doses of pearl millet for 7 d and on a steady-state day with 30 min time difference gliclazide was administered and blood samples were collected at different time intervals and were analyzed for blood glucose.

Collection of blood samples:

Blood samples were collected from the retroorbital plexus of the rats in a meticulous and standardized procedure. A delicate glass capillary was gently inserted into the inner angle of the eye, gliding under the eyeball at a 45° angle and traversing over the bony socket to delicately rupture the fragile venous capillary within the ophthalmic venous plexus. Blood samples were systematically collected at specified time intervals (0, 1, 2, 3, 4, 6, 8, 10, and 12 h) from all the groups of rats following the administration of the diet. Approximately 0.2 ml of blood was collected at each time point. The collected blood samples were then transferred into Eppendorf centrifuge tubes (1.5 ml, Tarson). Subsequently, the serum was separated by centrifugation and aliquots of the serum samples (0.1 ml) were transferred using an automated pipette. Immediate analysis of blood glucose levels was conducted utilizing the Glucose Oxidase/Peroxidase (GOD/POD) method. This rigorous and systematic procedure ensured precise and reliable measurements, facilitating a comprehensive understanding of the temporal dynamics of blood glucose levels in response to the administered millet diet over the specified time intervals. HbA1c (Ion exchange resin method) and insulin levels (Invitrogen Enzyme Linked Immunosorbent Assay (ELISA) kit) were estimated at each peak hour.

Bioanalytical method:

Plasma concentrations of gliclazide were determined using a Waters® 2487 High-Performance Liquid Chromatography (HPLC) unit equipped with an LC-20AD solvent delivery module, an SPD-20A UV detector, a Kromasil 100-5C18 column (100 mm×4.6 mm, 5 µm) and is in operation at 230 nm. An isocratic mobile phase consisting of a mixture of acetonitrile, methanol, and water (40:35:25, v/v/v) was used to separate analyte from endogenous components and delivered at a flow rate of 1.00 ml/min. All samples were vortexed for 10 s before addition. A 100 µl aliquot of serum sample was mixed with 50 µl internal standard working solution (50 µg/ml ibuprofen). To this was added 1 ml of methanol. After vortexing for 60 s and centrifugation at 4000 revolutions per minute (rpm) for 15 min, the supernatant was transferred to a 5 ml glass tube and evaporated at 45° under a gentle stream of nitrogen. The dried extract was reconstituted with 100 µl methanol and a 50 µl aliquot was injected into the HPLC system. Gliclazide and IS were eluted at 5.7±1 and 8.6±1 min respectively.

Statistical analysis:

The results were compared using two-way Analysis of Variance (ANOVA) and Bonferroni post-test to find statistical significance, ***significant at $p<0.001$; **significant at $p<0.01$; *significant at $p<0.05$ compared to control. The pharmacokinetic parameters were analyzed by using PKSolver software.

RESULTS AND DISCUSSION

Millet is an excellent source of fiber, which is known as complex unavailable polysaccharides[11]. They also contain health-promoting phytochemicals such as polyphenols, lignans, phytosterols, phytoestrogens and phytocyanins. These compounds act as antioxidants, immune modulators and detoxification agents that help protect against age-related degenerative diseases such as cardiovascular disease, diabetes, cancer, etc.,[12]. In addition to phytochemicals, millets contain several essential nutrients, vitamins, minerals and fatty acids that may also help prevent degenerative and nutritional diseases. Dietary fiber plays a vital role in promoting health by swelling the intestines, increasing small intestinal transit time and reducing the rate of glucose

absorption[13]. This can be beneficial in managing certain types of diabetes, such as non-insulin dependent diabetes mellitus. Sulphonylureas (SUs) are often recommended as a common adjunct to metformin, which is used as first-line treatment for T2DM[14]. These drugs are widely used in Southeast Asia due to their effectiveness and affordability. Among SUs, gliclazide has been shown to provide consistent glycemic control while causing fewer hypoglycemic episodes. It also has long-term micro- and macro-vascular benefits. This peer review highlights the role of SUs, specifically gliclazide in achieving safe and effective glycemic control in T2DM[15]. Millets, which are grains contain high amounts of phytic acid, which reduces the digestibility of carbohydrates and moderates postprandial blood glucose levels[16]. These grains also have prebiotic components that are metabolized by native bacteria in the human gut to produce beneficial short-chain fatty acids and probiotics that have anti-diabetic properties. Millet is particularly rich in resistant starch, which can slow gastric emptying and lower blood glucose levels after consumption[17].

The study initially involved normal rats and gliclazide 1 mg/kg was selected for interaction studies. The decision was based on previous research conducted by various authors on drug-drug interactions and drug-food interactions in rats[18]. Their research showed that a dose of 1 mg/kg was effective in reducing blood glucose levels in normal rats. The results of the study showed that gliclazide produced a biphasic reduction of blood glucose. It reduced the blood glucose levels by 30.9 % at 2 h and 19.53 % at 6 h as indicated in fig. 1. The maximum reduction at 2 h may be attributed to the initial rapid release of insulin (phase I) stimulated by gliclazide and its ability to increase the sensitivity of pancreatic β-cells to glucose. However, gliclazide did not affect the prolonged insulin release (phase II)[19]. The reduction seen at 6 h may be attributed to gliclazide's ability to increase the sensitivity of peripheral tissues to insulin. Gliclazide is metabolized to several metabolites by hepatic cytochrome P450 3A4 and 2C9 isoenzymes and is eliminated in urine[20]. Some of it is eliminated through the biliary route, which involves enterohepatic circulation in rats[21]. The reabsorption of gliclazide eliminated through the biliary route may be responsible for a second peak in its hypoglycemic effect in normal rats.

In this study, gliclazide was used as a representative drug of SUs to examine drug interactions. The study focused on the effects of gliclazide-induced hypoglycemia, which was observed by administering 1 mg/kg b. wt in laboratory conditions. The dosage produced a 30.90 % and 19.53 % reduction in blood glucose levels at 1 h and 6 h, respectively. Finally, rats treated with Pearl Millet Diet (PEMD) 30 and PEMD 60 demonstrated a 24.79 % and 29.74 % reduction at 3 h in blood glucose levels, respectively. These dosages were selected for further experimentation and the results were documented in fig. 1 and fig. 2.

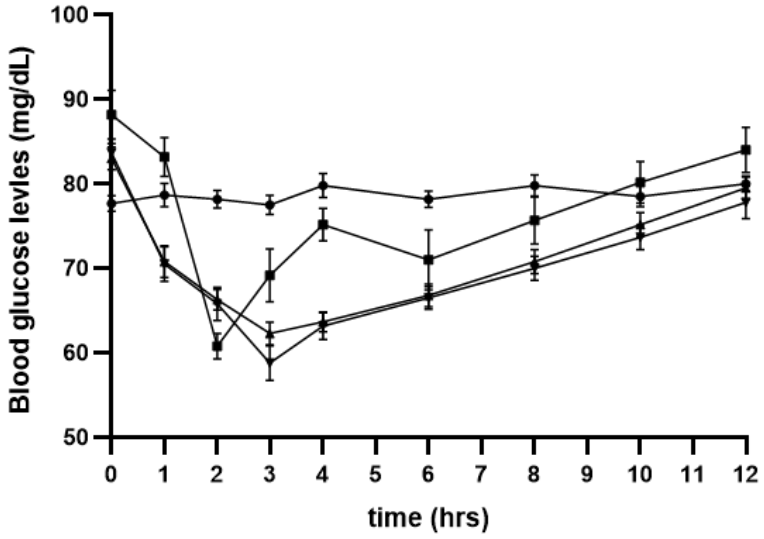

Fig. 1: Effect of gliclazide and PEMD on blood glucose levels in normal rats
Note: (—●—): Normal; (—■—): Gliclazide 1 mg/kg; (—▲—): PEMD (30 %) and (—▼—): PEMD (60 %)

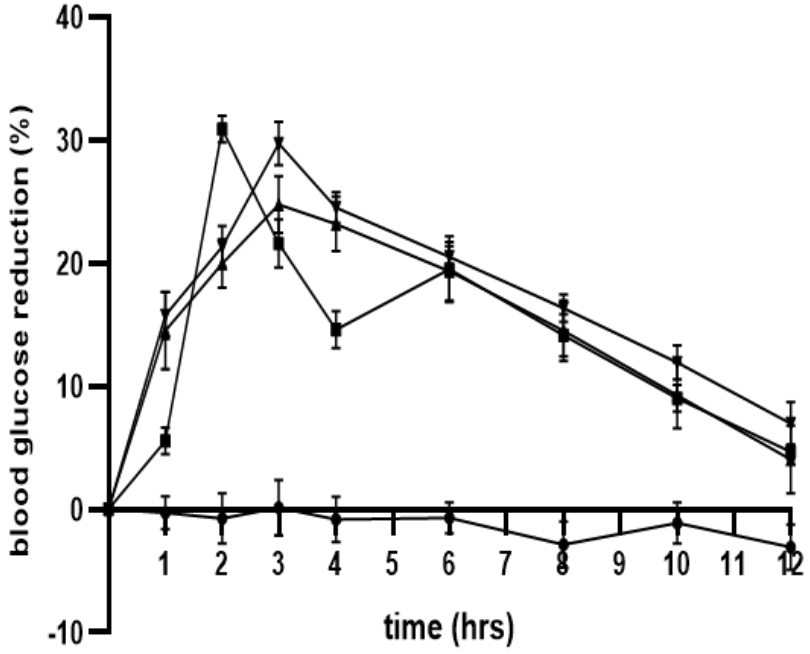

Fig. 2: Effect of gliclazide and PEMD on percentage blood glucose reduction in normal rats
Note: (—●—): Normal; (—■—): Gliclazide 1 mg/kg; (—▲—): PEMD (30 %) and (—▼—): PEMD (60 %)

Finally, gliclazide+PEMD-Single Dose (SD) did not produce any significant changes (31.38 % at 2 h and 17.38 % at 6 h), but there was a significant reduction of blood glucose levels at the second peak hour (6 h) with 24.71 % with gliclazide+PEMD-repeated dose (MD) compared with gliclazide alone treatment as shown in fig. 3 and fig. 4.

Gliclazide+PEMD-SD showed a significant enhancement of serum gliclazide to 13.67 µg/ml and 10.10 µg/ml at 2 h and 6 h, respectively as shown in Table 1. The pharmacokinetic analysis explained changes in elimination half-life ($t_{1/2}$), Time to peak drug concentration (T_{max}), maximum plasma Concentration (C_{max}) and Mean Residence Time (MRT) corresponding to the serum gliclazide levels with all three millet diets (Table 2). These results can aid in understanding the mechanism of how gliclazide levels are influenced by combined therapy. The serum insulin and HbA1c levels were assessed during peak hours to determine the effect of combining them. However, there was no significant difference in serum insulin and HbA1c levels in millet combinations as shown in Table 3.

Pharmacodynamic interactions are possible with simultaneous administration of pearl millet and gliclazide may be due to a potential synergistic antidiabetic effect. In general, pearl millet is classified as a low GI food due to its high fiber content[22]. GI assesses how much the carbohydrate content of food affects the rate and extent of change in postprandial blood glucose concentration. Many theories support the hypoglycemic effects of pearl millet, such as the theory that pearl millet is rich in phytate and phenolic compounds reduces fasting hyperglycemia and attenuated postprandial blood glucose response in rats. Phenolic compounds are also known to increase insulin activity and pearl millet regulates intestinal GLUTs, increases muscle glucose uptake and decreases hepatic gluconeogenesis[23]. A possible mechanism of interaction is the inhibition of CYP3A4 by the millet diet leading to a decrease in the metabolism of gliclazide and subsequently to an increase in the concentrations of gliclazide and its bioavailability[24]. Overall, this study reasonably confirms that inhibition of CYP3A4 by millet indeed leads to increased concentrations of gliclazide and subsequently to increased glucose reduction.

In conclusion, the study found that when pearl millet and gliclazide are given together, there are significant interactions between them. These interactions may be due to the combined effects of their pharmacodynamic activity and metabolic pharmacokinetic interactions. To avoid potential hypoglycemia, doctors should be aware of these interactions and adjust the dosage of gliclazide accordingly.

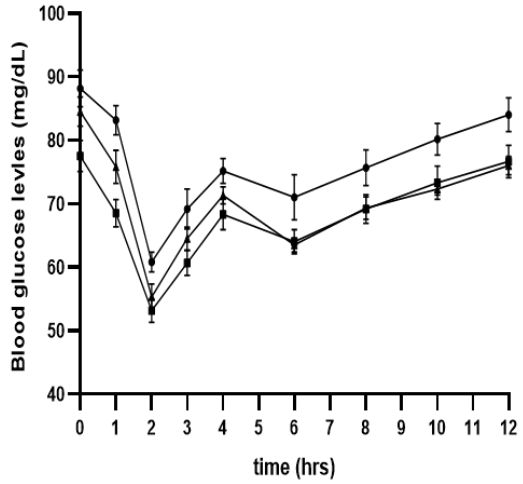

Fig. 3: Effect of gliclazide and combination of PEMD 60 on blood glucose levels of single and multiple dose study in normal rats
Note: (—■—): Gliclazide+PEMD SD; (—▲—): Gliclazide+PEMD MD and (—●—): Gliclazide 1 mg/kg

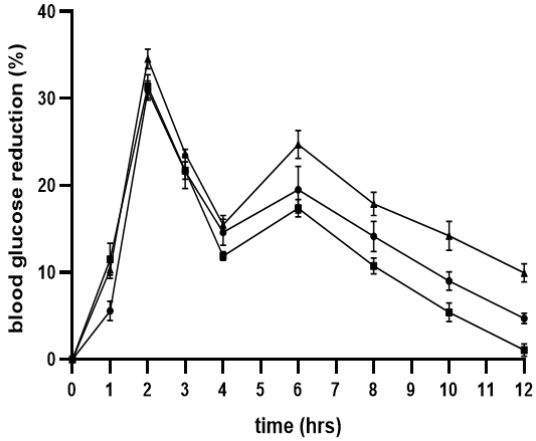

Fig. 4: Effect of gliclazide and combination of PEMD 60 on percentage blood glucose reduction of single and multiple dose study in normal rats
Note: (—■—): Gliclazide+PEMD SD; (—▲—): Gliclazide+PEMD MD and (—●—): Gliclazide 1 mg/kg

TABLE 1: SERUM GLICLAZIDE LEVELS OF RATS TREATED WITH GLICLAZIDE AND COMBINATION OF PEMD 60 IN SINGLE AND MULTIPLE DOSE STUDIES IN NORMAL RATS

	Serum gliclazide levels		
	Gliclazide	Gliclazide+pearl	
	Alone	SD	MD
0	0.00±0.00	0.00±0.00^{ns}	0.00±0.00^{ns}
1	7.90±1.10	2.88±0.32**	8.23±0.23^{ns}
2	12.03±1.10	11.46±0.45^{ns}	13.67±0.42
3	10.76±1.98	9.36±0.27	10.17±0.35^{ns}
4	7.77±1.52	7.80±0.33^{ns}	8.08±0.44*
6	9.04±2.69	9.14±0.36^{ns}	10.10±0.27*
8	6.89±1.74	6.23±0.29^{ns}	7.98±0.33^{ns}
10	5.33±1.08	5.13±0.42^{ns}	6.93±0.38*
12	4.89±0.61	3.71±0.39	5.45±0.41^{ns}

Note: ns: not signified; ^{ns}p>0.05, *p>0.05, **p<0.01, ***p<0.001, significance followed by two-way ANOVA multiple comparison test with gliclazide

TABLE 2: PHARMACOKINETIC PARAMETERS OF RATS TREATED WITH GLICLAZIDE AND A COMBINATION OF PEMD 60 IN SINGLE AND MULTIPLE-DOSE STUDIES IN NORMAL RATS

Parameter	Pharmacokinetic parameters			
	Unit	Gliclazide	PEMD-SD	PEMD-MD
Lambda_z	1/h	0.11±0.002	0.14±0.001	0.10±0.003
$t_{1/2}$	h	6.60±0.005	4.78±0.004	6.96±0.002
T_{max}	h	2.00±0.011	2.00±0.017	2.00±0.13
C_{max}	µg/ml	12.03±0	11.46±0	13.67±0*
T_{lag}	h	0.00±0.02	0.00±0.04	0.00±0
C_{last_obs}/C_{max}		0.41±0.003	0.32±0.004	0.40±0.002
AUC_{0-t}	µg/ml.h	89.76±0.11	80.11±0.18	99.66±0.13*
AUC_{0-inf_obs}	µg/ml.h	136.32±1.7	105.70±1.4	154.38±1.4*
$AUC_{0-t/0-inf\_obs}$	µg/ml.h	0.66±0.004	0.76±0.005	0.65±0.003
$AUMC_{0-inf\_obs}$	µg/ml.h^2	1497.17±31.31	940.84±23.54	1773.60±34.67*
MRT_{0-inf_obs}	h	10.98±0.07	8.90±0.05	11.49±0.04*
Vz/F_obs	(mg)/(µg/ml)	0.70±0	0.65±0	0.65±0
Cl/F_obs	(mg)/(µg/ml)/h	0.07±0	0.09±0	0.06±0

Note: ^{ns}p>0.05, *p>0.05, significance followed by two-way ANOVA multiple comparison test with gliclazide

TABLE 3: MEAN SERUM INSULIN (µIU/ml) AND HbA1C WITH MEAN SERUM GLUCOSE LEVEL (mg/dl) IN GLICLAZIDE, PEMD AND SINGLE AND MULTIPLE DOSE COMBINATIONS AT PEAK HOURS OF BLOOD GLUCOSE REDUCTION

Group	Time (h)	Mean serum glucose levels (mg/dl)	Serum insulin (µU/ml)	HbA1C (mg/dl)
Gliclazide	2 h	60.83±1.53	10.33±0.18	5.09±0.09
	6 h	71.00±3.58	9.25±0.23	5.58±0.17
PEMD 60	3 h	58.83±2.05	9.27±0.03	6.06±0.12
Gliclazide+PEMD (SD)	2 h	53.17±1.84	9.72±0.02	5.64±0.09
	6 h	55.33±2.03	7.89±0.43	6.15±0.33
PEMD+Gliclazide (MD)	2 h	64.00±1.94	10.13±0.14	5.14±0.28
	6 h	63.50±1.12	9.07±0.13	5.77±0.19

Conflict of interests:

The authors declare that there is no conflict of interest.

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