Pharmacodynamic Drug Interaction of Gliclazide and Mexiletine in Rats

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Summary

The present study is planned to find out the pharmacodynamic drug interaction of mexiletine (class Ib Antiarrhythmic drug) on hypoglycemic activity of Gliclazide (Second generation sulphonylureas), which is used in type-II diabetes management in humans. This study were conducted in normal rats, alloxan induced diabetic rats with oral administration of selected doses of gliclazide, mexiletine and their combinations, with adequate washout period in between the treatments. Blood samples were collected from rats by retroorbital puncture at regular intervals of time. All the blood samples were analyzed for glucose by GOD-POD method. Gliclazide produce hypoglycemia / antihyperglycemia in normal and diabetic rats with peak activity at 1hr and 8hr and mexiletine produces hypoglycemia when given alone and in combination, it increased the effect of gliclazide at the first peak and at the second peak in normal and diabetic rats.

Key words: Drug Interactions, Gliclazide, Mexiletine, GOD-POD method.

Introduction

Diabetes is a condition in which the body either does not produce enough insulin or can't utilize insulin properly. It is a group of syndrome characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins and an increased risk of complications like atherosclerosis, dislipidemia and other cardiac disorders increases morbidity and mortality [1].

Among diabetics, approximately 95 % of patients are type II diabetes mellitus, where as 5 % of patients have type I diabetes mellitus. Patients with diabetes mellitus leads to cardiac disorders like arrhythmias and angina are to occur, as a result the use with antiarrhythmic or antianginal drugs along with antidiabetic drugs is also common[2,3].In such situation, there may be chances for drug-drug Interactions between antidiabetic and antiarrhythmic drugs. Sulphonylureas are the drugs of choice in the treatment of type-II diabetes. Currently gliclizide, a second generation sulphonyl urea, was preferred in therapy because of its selective inhibitory activity toward pancreatic K^+ATP channels [4], low incidence of producing severe hypoglycemia [5] and other haemobiological effects [6].

It is well established that sulphonylureas produce insulin secretion and improve tissue utilization of glucose at cellular level which was responsible for lowering of blood glucose level. Sodium channel blockers are one group of drugs used for the treatment of arrhythmia (mexiletine: class-Ib Antiarrhythmic drug) is widely used in the treatment of arrhythmia, the concomitant administration of gliclazide with mexiletine in diabetes associated with arrhythmias may result in drug-drug interaction with enhanced/decreased gliclizide activity, which is unwanted. The study is planned to establish the safety of the drug combination in animal models with respect to blood glucose level.

Material and Methods:

Gliclazide	:	Dr.Reddy's laboratories; Hyderabad.
Mexiletine Hydrochloride	:	German Remedies ltd; Mumbai
Glucose Kits (GOD/POD method)	:	Manufacture by Span Diagnostics. Were produced from local suppliers.
Alloxan Monohydrate.	:	Sd.fine-chem Limited, Mumbai.

Animals:

Albino rats of either sex, weighing between 160-280 grams procured from Sainath-agencies (Approved by CPCSEA), Hyderabad; were use in the study. Animals were maintained under standard laboratory conditions at ambient temperature of 25 ±2ºc with 12 hours light/12-hours dark cycle. They were fed with standard pellet diet (Hyderabad, India) and water ad Libitum. Animals were fasted for 18 hours before experiment and during the experiment they were withdrawn from food and water .The prior approval for conducting the experiments in rats were obtained from our Institutional Animal Ethics Committee and our lab approved by CPCSEA, Government of India, Regd. No. [IAEC/SUCP/05/2009].

Study in normal rats:

A group of six albino rats weight between 200-280 gm were administered with 2 mg/kg bodyweight of gliclazide, orally (gliclazide 1mg/ml solution in distill water, by adding few drops of N/10 NaoH solution to solubilizing).The same group was administered with 7.2 mg/200gm body weight mexiletine dose for animals calculated from human dose [12], orally after a washout period of one week. The same group was also administered with 7.2 mg/200gm body weight mexiletine 30 min prior to 2mg/kg bodyweight gliclazide, after a further washout period of one week. Blood samples were withdrawn from retro orbital puncture [7] at 0, 1, 2, 3, 4, 6, 8, 10, 12&16 hrs intervals. Blood samples were analyzed for blood glucose levels by GOD-POD method [8] using commercial glucose kits (span diagnostics).

Induction of diabetes:

Diabetes was induced by the administration of alloxan in two doses, i.e., 100mg and 50 mg/kg body weight, Intraperitoneally (I.P) for two consecutive days [9].

Study in diabetic rats:

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 groups.

Data & statistical analysis:

Data were expressed as mean ± Standard Deviation (SD).The significance was determined by applying student's paired t test by using GraphPad Prism 5.

Results

Gliclazide produced biphasic hypoglycemic activity with maximum reduction of Blood glucose level 46.7±5.6 & 42.5±4.04 after 1 hr and after 8hr in normal rats and antihyperglycemic activity with maximum reduction of Blood glucose 47.9±1.17 and 44.3±2.1 after 1hr and 8 hrs in diabetes rats respectively.Mexiletine alone produced 33.1±4.28% and 34.3±1.26% decrease in the blood glucose in normal and diabetic rats after 6 hr.When Gliclazide given in combination with mexiletine produced enhanced hypoglycemic effect with maximum reduction of 52.14 ± 6.78% & 50.93±4.58 % and 53.5±0.86% & 51±0.46% in blood glucose in normal and diabetic rats after 1 hr and 8 hrs.

Table: I: Mean percent blood glucose reduction after oral administration of gliclazide, mexiletine and their combination (Gliclazide+mexiletine) in normal rats (N=6)

Time(hr)	Gliclazide	Mexiletine	Gliclazide+ Mexiletine
0	0	0	0
1	46.7±5.6	20.36±7.69	52.14±6.78***
2	32.8± 8.0	26.9±4.01	47.3±5.3***
3	28.3± 11.31	22.5±5.87	35.36±6.17**
4	17.4±2.88	31.9±8.4	20.3±5.22**
6	30.64±10.45	33.1±4.28	45.62±3.9***
8	42.5±4.04	14.7±2.6	50.93±4.58**
10	28.4±4.1	10.3±4	31.6±3.2
12	11.7±9.5	7.6±3.184	13.1±3.3**
16	5.22±2.28	3.425±1.7	7.61±0.427*

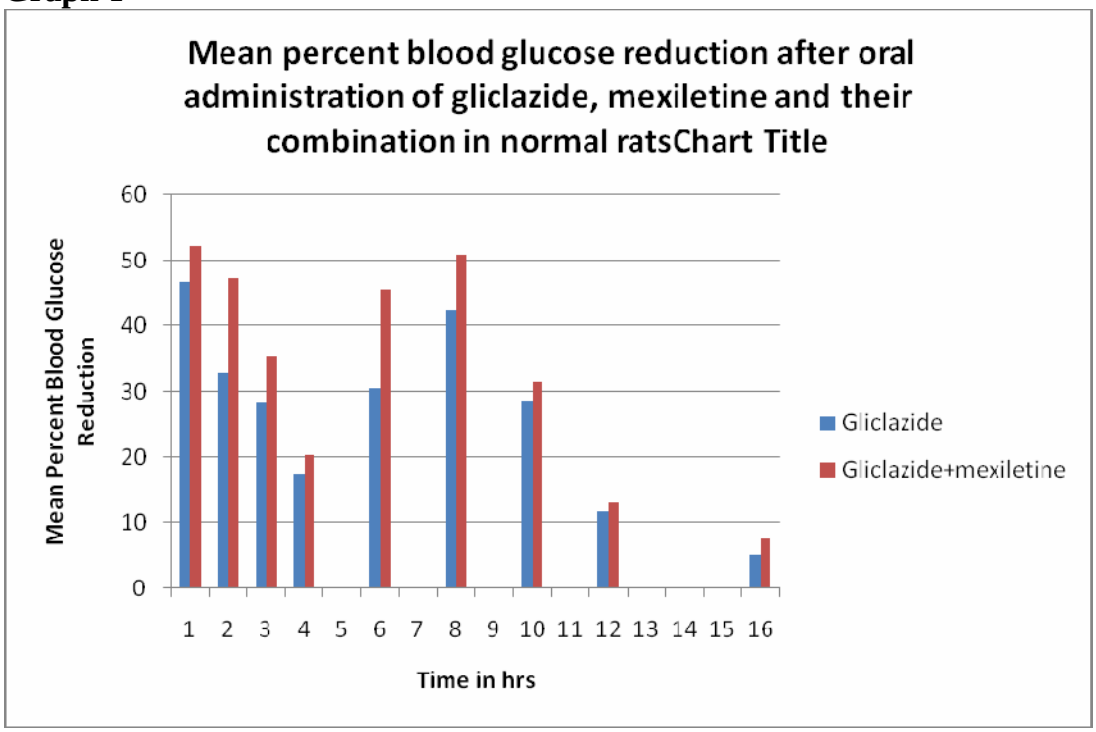
Mean± SEM; ***Significant at P< 0.0001; **Significant at P< 0.001; *Significant at P< 0.05 compared to gliclazide control; Gliclazide+ Mexiletine in normal rats

Table: II: Mean percent blood glucose reduction after oral administration of gliclazide, mexiletine and their combination (Gliclazide+mexiletine) in diabetic rats (N=6)

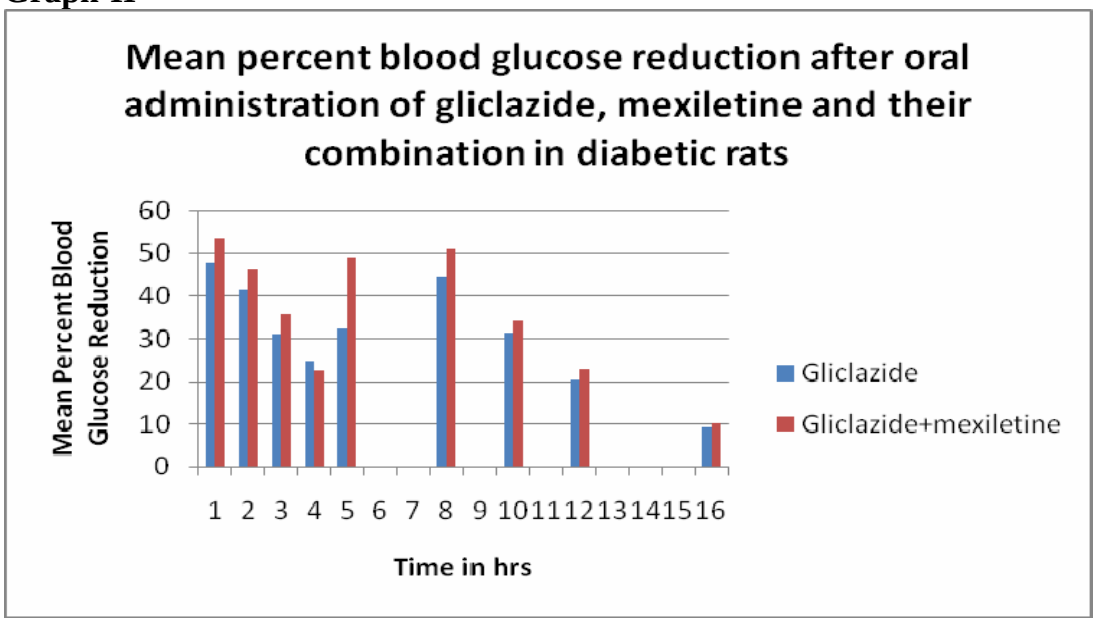
Time(hr)	Gliclazide	Mexiletine	Gliclazide+ Mexiletine
0	0	0	0
1	47.9±1.17	20.6±1.0	53.5±0.86***
2	41.7±2.28	28.7±2.53	46.2±2.23***
3	31.1±2.16	29.5±1.4	35.8±1.2***
4	24.7±2.22	30.3±5.27	22.5±2.78***
6	32.5±3.58	34.3±1.26	49.1±1.08***
8	44.3±2.1	18.5±1.22	51±0.46***
10	31.5±3.1	14.6±1.2	34.2±1.3
12	20.3±2.35	12.3±1.27	22.9±3.54***
16	9.25±2.61	6.9±1.66	10.1±1.08***

Mean± SEM; ***Significant at P< 0.0001; **Significant at P< 0.001; *Significant at P< 0.05 compared to gliclazide control; Gliclazide+ Mexiletine in Diabetic rats

Graph-I



Graph-II



Discussion

Diabetes is group of syndrome require multiple drug therapy to manage either a single disease or simultaneous occurring different diseases. Drug interactions observed in clinical practice and the mechanism of interactions are evaluated in animal models. We studied the influence of mexiletine on the pharmacodynamics of gliclazide in normal and diabetic rats. The normal rat model served as to quickly identify the interaction and the diabetic rat model served to validate the same response in the actually used condition of the drug. The gliclazide produced biphasic response in rat model may be due to its enterohepatic circulation in rats [13, 14] and humans [15].Gliclazide is known to produce hypoglycemic activity by both pancreatic (insulin release by K^+ channel inhibition in the β cells) and Extrapancreatic (tissue uptake of glucose) mechanism. Mexiletine produced hypoglycemic effect when administered alone and also enhanced the gliclazide induced hypoglycemic effect. The interaction may be due to mexiletine induce hypoglycemia is thought to be due to pancreatic β cells over production of insulin because of mexiletine (a sodium channel blocker) inhibiting I_{Na} and increasing the concentration of intracellular ATP by lowering the consumption of ATP, thereby inhibiting I_{KATP} causing depolarization of the β-cell followed by activating calcium channels, increases intracellular calcium concentration followed by an increase in insulin release and gliclazide also produces hypoglycemic action by release of insulin from β cells of islet of langerhans of pancreas and also by increase glucose uptake at cellular level [16]. The interaction studies showed a similar fall of blood glucose even in diabetic rats and also enhancement of gliclazide effect. The study of interaction of mexiletine with gliclazide produced statistically significant pharmacodynamic interaction in normal rats.Mexiletine produced perse hypoglycemia when administered alone and enhanced the effect of gliclazide. The interaction studies of mexiletine in diabetic rats produced similar results as observed in normal rats.

Conclusion

The interaction observed to be pharmacodynamic interaction. Since the interaction was observed in normal and diabetic rats, it is likely to occur in humans also. So, the combination of gliclazide and mexiletine should be use with caution in clinical practice.

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