ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Pharmacodynamic drug interaction of mexiletine with metformin in rats

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ABSTRACT

The present study is aimed to explore the pharmacodynamic interaction of mexiletine (class Ib antiarrhythmic drug) with metformin in normal and diabetic rats. The doses of mexiletine and metformin calculations were based on therapeutic dose of human extended to animals [8]. The diabetes was induced by alloxan monohydrate (aqueous solution) in 2 doses of 100 mg / kg and 50 mg / kg b.wt I.P for two consecutive days. The blood glucose was measured by GOD/POD method. The mexiletine produced hypoglycaemia in normal rats and antihyperglycaemia in diabetic condition. Mexiletine enhanced antihyperglycaemic activity of metformin in diabetic rats.

Key words: Drug interactions, Metformin, Mexiletine, GOD/POD method and diabetes.

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ISSN: 0975-8585

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by rise in blood glucose level called hyperglycaemia. Which requires careful management of its therapy with respect to blood glucose levels since both hyperglycaemia and hypoglycaemia are unwanted. It is of two types, type 1 accounting for 5% prevalence and type 2 for 95% prevalence among diabetics [1, 3].

According to WHO 40-60% type 2 diabetics are obese patients. Type 2 diabetic subjects have an increased predilection for developing cardiac disease and other atherosclerotic manifestations [19]. The prevalence of coronary artery disease was 21.4% among diabetic subjects compared to 9.1% in subjects with normal glucose tolerance [10, 18].

In such a situation there may be chances for drug – drug interactions between antidiabetic and antiarrhythmic drugs. These drug – drug interactions may be beneficial (useful) or harmful. So there is a need for monitoring drug therapy in polypharmacy in order to have better therapeutic effect with lower rate of risk. Drug – drug interactions may be of pharmacokinetic or pharmacodynamic in nature. The study of mechanism of drug interactions will be of much value in therapy that helps in selecting the drug combinations and ensuring safety and efficacy. Metformin is a widely and more commonly used biguanide. Antiarrhythmic drugs like sodium channel blockers are widely used for the treatment of arrhythmias among the sodium channel blockers mexiletine is widely used. Mexiletine is metabolized by CYP450 2D6, CYP450 1A2, CYP450 3A4 and the metabolites are excreted in urine completely [4, 20].

Metformin is not metabolized [12, 15] and it is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion [13, 16]. To find out the safety and mechanisms of interaction of such drug combinations the present work was planned in normal and diabetic rats with respect to blood glucose level. The outcome of the work provides information which has clinical utility.

MATERIAL AND METHODS

Metformin	:	Dr.Reddy's Laboratories; Hyderabad.
Mexiletine	:	German Remedies Ltd; Mumbai.
Glucose kits	:	Span Diagnostics Ltd.,
Rats (Albino rats)	:	Sainath Agencies, Hyderabad. (CPCSEA Approved)
Alloxan Monohydrate	:	Sd.Fine-chem limited, Mumbai.

Animals:

Albino rats of both sex procured from Sainath- agencies (Approved by CPCSEA), Hyderabad; weighing between 180-280 grams were use in the study. Animals were maintained under standard laboratory conditions at atmospheric temperature of 25 ±2ºc with 12 hours light/12-hours dark cycle. They were fed with standard pellet diet 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 was

obtained from our Institutional Animal Ethics Committee and our lab approved by CPCSEA, Government of India, and Regd. No. [IAEC/SUCP/05/2009].

Study in normal rats:

A group of six albino rats weight between 200-280 gm were administered orally with standard metformin (dissolved in distilled water 2TD 18 mg/200g b.wt orally and the blood samples were analysed for blood glucose. After a wash out period of 1 week the same group was given mexiletine 7.2 mg/200 g b.wt only. A different group of six rats were administered with mexiletine 7.2 mg/200 g b.wt and after 30 min 18 mg/200 g b.wt metformin (2TD) was given. After1week the same group was continued with mexiletine for next 7 days with regular feeding on the 8th day after 18h fast they were given the combined treatment (mexiletine + and after 30 mints metformin) and were analyzed for blood glucose. The blood samples were collected from retro orbital puncture [21] into the Eppendroff's centrifuge tubes (1.5 ml, Tarson) at 0, 1, 2, 3, 4, 6, 8, 10 and 12 h intervals from all the groups of rats after the administration of last drug. Each time about 0.4 ml of blood was collected. The serum was separated by centrifuging the samples and the serum samples (0.1ml) were transferred using automated pipette and were analyzed immediately for blood glucose by GOD/POD method [11] by using commercial glucose kits (span diagnostics).

Induction of diabetes:

Diabetes was induced by the administration of alloxan (40 mg/ml solution in distilled water was prepared. After two days of acclimatization in the laboratory the rats were administered with 100mg/kg body weight of alloxan by I.P route [7, 17]. After the injection they were provided with 10% dextrose solution through feeding bottles to prevent sudden hypoglycemia, because of sudden release of insulin from destroyed cells. Standard pellet diet provided in adequate quantity during the induction of diabetes. An additional dose of alloxan 50 mg/kg body weight was administered by Intra Peritoneal route if rise of blood glucose was not seen. Standard pellet food and dextrose solution was provided as described above. After 2 days, the blood glucose was estimated and rats with blood glucose above 250mg/dl were considered suitable for experimentation [6]. 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 shown as mean ± Standard Deviation (SD).The significance was determined by applying student's paired t test by using GraphPad Prism 5.

RESULTS AND DISCUSSION

The antidiabetic drug metformin, 2 TD (18 mg / 200g body weight) produced 31.30 ± 03.50 % peak reductions at 6 hr. Mexiletine induced hypoglycemia on administering TD dose

7.2 mg / 200 g body weight with peak activity of 33.10 ± 04.28 % reduction in blood glucose at 6 h. Metformin in combination with mexiletine produced peak reduction of 40.43 ± 02.20 % at 6^{th}h. Compared to the matching control response of metformin the combination enhanced the glucose reduction. On chronic treatment with mexiletine the combination produced peak blood glucose reduction of 42.15 ± 02.62 % at 6^{th}h. Compared to metformin matching control or single dose combination, the multiple dose combination with marginally enhanced the glucose reduction in normal rats.

Metformin, 2TD (18 mg / 200 g body weight) produced reduction in blood glucose with a peak activity of 40.22 ± 01.58 % at 6 h, Mexiletine induced antihyperglycaemic activity on administering doses TD 7.2 mg / 200 g bodyweight, produced 34.30 ± 01.26 % reductions in blood glucose with a peak at 6 h in diabetic rats. Metformin in combination with mexiletine produced peak reduction of 46.11 ± 03.78 % at 6^{th}h. On chronic treatment with mexiletine the combination produced peak blood glucose reduction of 46.78 ± 04.98 % at 6^{th}h. Compared to metformin matching control or single dose combination, the multiple dose combination with marginally enhanced the glucose reduction in diabetic rats.

The doses of selected drugs were administered to rats / rabbits were calculated based on human therapeutic doses extrapolated to animals based on body surface area using the formula in rat dose = 0.018 × human therapeutic dose / rabbit dose = 0.07 × human therapeutic dose[8]. Such doses were taken as therapeutic doses (TD) depending on the effect of such doses particularly with antidiabetic drugs, suitable doses that produced 30-45 % reduction were arrived at and these doses were employed for the interaction studies.

Metformin is a widely used drug in the treatment of Type-1 as well as Type-2 diabetes. It has multiple antidiabetic effects, such as inhibition of gluconeogenesis, delay of gastrointestinal absorption of glucose, reduction in food intake (or) prevents body weight gain in obese patients with type-2 diabetes and in animal models of obesity [2, 18]. Metformin increases plasma active glucagon – like peptide – 1 (GLP – 1) in obese and non diabetic subjects [9]. The hypoglycemic action seen with metformin might be due to the above mechanisms. It produced dose dependent effect and 2 TD dose was selected as standard dose since it produced 30-45 % reduction in blood glucose. It was mentioned that metformin does not produce hypoglycaemia in normal condition in humans. But in the present study in rats, it was found to produce hypoglycaemia in normal condition also. It appears that rats were more sensitive to metformin action than humans and there exist species variation in metformin response [5]. In our earlier studies it was observed that rats were more sensitive than rabbits in responding to hypoglycaemic activity of gliclazide supporting species variation in blood glucose response to drugs [14].

Mexiletine is antiarrhythmic drugs with sodium channel blockade and induce hypoglycemia. It is thought to be due to pancreatic β cell over production of insulin because sodium channel blockers inhibit sodium ions and increase the concentration of intracellular ATP by lowering the consumption of ATP, thereby inhibiting ionic K^+ATP causing depolarization

ISSN: 0975-8585

of the β cells followed by activating calcium channels, increase calcium concentration followed by increase in insulin released.

In combination with mexiletine, metformin enhanced the hypoglycemic activity and it may be due to their added pharmacodynamic activity. Metformin is not metabolized by hepatic microsomal enzyme system and is excreted unchanged. Hence the enhancement in metformin action may not be due to metabolic competitive inhibition exerted by disopyramide / mexiletine.

The single and multiple dose effect of the antiarrhythmic drug on metformin was similar indicating that they did not affect the metabolism of metformin even on chronic administration. They also enhanced antihyperglycaemic activity of metformin in diabetic rats.

Table-1: Percentage blood glucose reduction after oral administration of Metformin(2TD), Mexiletine alone, single dose of mexiletine and metformin 18 mg / 200 g b.wt & multiple dose of mexiletine and metformin 18 mg / 200 g b.wt in normal rats (n=6).

Time (h)	Percent blood glucose reduction Mean ±SD			
	Metformin (2TD)	Mexiletine(TD)	Single dose combination	Multiple dose combination
1	11.35 ± 00.97	20.36 ± 07.69	13.30 ± 02.43	14.26 ± 01.28
2	19.11 ± 04.08	26.90 ± 04.01	23.38 ± 02.10	25.40 ± 01.59
3	23.42 ± 03.49	22.50 ± 05.87	32.38 ± 03.30	33.18 ± 01.21
4	28.26 ± 04.60	31.90 ± 08.40	38.95 ± 02.82**	40.15 ± 01.36***
6	**31.30 ± 03.50**	**33.10 ± 04.28**	**40.43 ± 02.20*** **	**42.15 ± 02.62*** **
8	24.37 ± 02.60	14.70 ± 02.60	33.48 ± 02.95*	34.32 ± 02.17*
10	18.24 ± 04.57	10.30 ± 02.80	23.45 ± 02.50*	26.36 ± 01.88**
12	11.35 ± 00.97	07.60 ± 03.18	14.45 ± 03.20	15.91 ± 02.48

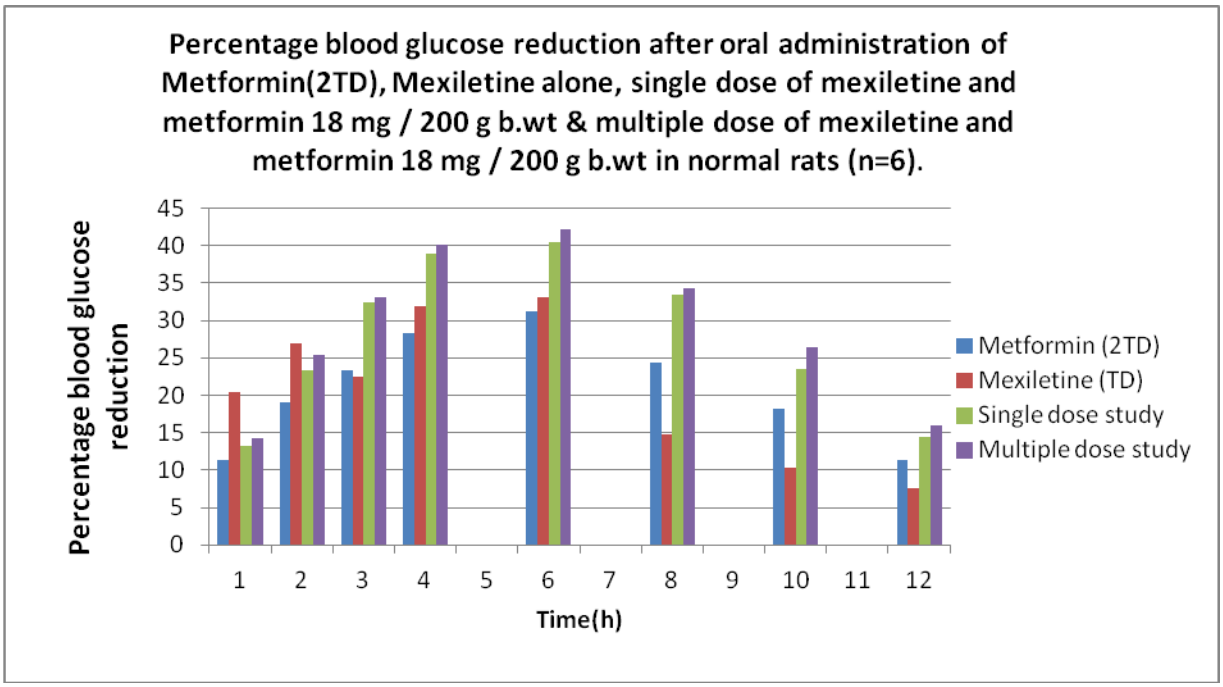
*** Significant at P<0.001; ** Significant at P< 0.01; *Significant at P<0.05 compared to control gliclazide

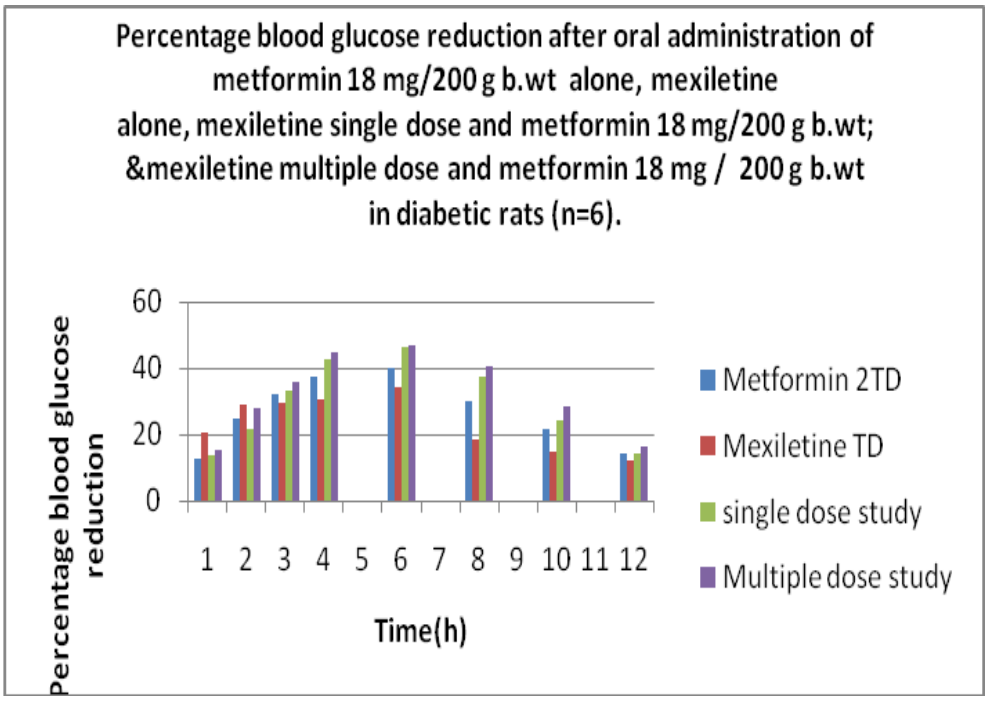
Table-2: Percentage blood glucose reduction after oral administration of metformin 18 mg/200 g b.wt alone, mexiletine alone, mexiletine single dose and metformin 18 mg/200 g b.wt; &mexiletine multiple dose and metformin 18 mg / 200 g b.wt in diabetic rats (n=6).

Time (h)	Percent blood glucose reduction Mean ±SD			
	Metformin(2TD)	Mexiletine	Single dose combination	Multiple dose combination
1	12.83 ± 01.19	20.60 ± 01.00	13.84 ± 01.48	15.40 ± 04.62
2	24.72 ± 03.52	28.70 ± 02.53	21.75 ± 01.48*	27.72 ± 05.15
3	31.98 ± 03.53	29.50 ± 01.40	33.17 ± 01.48	35.89 ± 03.38
4	37.16 ± 02.11	30.30 ± 01.80	42.71 ± 01.48*	44.93 ± 05.26**
6	**40.22 ± 01.58**	**34.30 ± 01.26**	**46.11 ± 03.78***	**46.78 ± 04.98***
8	29.81 ± 01.66	18.50 ± 01.22	37.35 ± 01.48**	40.44 ± 05.51***
10	21.72 ± 05.03	14.60 ± 01.19	24.35 ± 01.48	28.41 ± 02.54*
12	14.33 ± 02.48	12.30 ± 01.27	14.40 ± 01.48	16.32 ± 03.68

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

ISSN: 0975-8585





CONCLUSION

Hence the interaction observed between the metformin and mexiletine in both normal rats and diabetic rats might be pharmacodynamic interactions, it may occur in humans also. So, the combination of metformin and mexiletine should be use with caution in clinical practice.

ISSN: 0975-8585

ACKNOWLEDGEMENTS

The authors thank Dr.Reddy's Laboratories; Hyderabad and German Remedies Ltd; Mumbai for providing the gift sample of metformin and mexiletine respectively.

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