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Effects of Amiodarone on the Glucose Lowering Effect of Glimepiride: An Animal Experiment

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The purpose of the current study was to ascertain how the antiarrhythmic drug amiodarone, which was given to normal and diabetic rats in numerous doses over seven days, affected the hypoglycemic effect of glimepiride. Finding the medication interaction between glimepiride and amiodarone in rats was the aim of the study. Six healthy and six diabetic rats of both sexes participated in these investigations. Amiodarone (50 mg/kg body weight) and glimepiride (0.41 mg/kg) were the medication doses provided. Oral administration of the drug was used. Blood

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samples were taken from the tail vein at prearranged intervals, and the Glucose oxidase peroxidase method was applied to calculate the amount of glucose. The results showed that in both normal and diabetic rats, amiodarone, an antiarrhythmic drug, affected the hypoglycemic effect of glimepiride when administered alone or combined with glimepiride. i.e., in healthy albino rats the amiodarone given for a week, the onset of hypoglycemia with glimepiride was increased i.e., (from 16.58±0.61% to 27.89±0.62% at 1st hour), the duration and peak hypoglycemia were both prolonged i.e., (from 17.32±0.62% to 27.14±2.63%) and (from 46.77±0.52% to 60.67±0.67% at 8th hour respectively. In diabetic rats, the hypoglycemia's peak and duration increased i.e., (from 44.50±0.66% to 60.88±0.62% at the 8th hour) and (from 15.97±0.49% and increased to 28.52±1.21% post at 24 hours) respectively. This study suggests that in the case of amiodarone and glimepiride combined use, therapeutic drug monitoring is required in order to adjust the dose.

Keywords: Glucose oxidase and peroxidase GOD/POD method; amiodarone, drug-drug interactions; glimepiride.

1. INTRODUCTION

In recent times, there has been a rise in the use of class III antiarrhythmic medications, particularly the broad-spectrum antiarrhythmic agent amiodarone [1]. Wolff-Parkinson-White syndrome patients whose supraventricular tachycardias are resistant to other medications have found success using amiodarone to treat their arrhythmias [2]. Yet, the comparatively frequent appearance of serious and possibly fatal side effects has restricted the administration of amiodarone [3]. Diabetes mellitus is a chronic metabolic condition marked by elevated blood glucose levels, which may result from inadequate insulin secretion. [4]. In addition to stimulating the release of insulin from pancreatic beta cells, glimepiride, a member of the sulphonylurea class, can also work through extrapancreatic pathways [5]. It is a helpful, affordable treatment choice because it reduces the levels of glycosylated haemoglobin, postprandial glucose, and fasting plasma glucose, which is beneficial for managing type 2 diabetes mellitus [6]. Because of various multiple medical conditions, those suffering from type 2 diabetes often need polypharmacy treatment. The possibility that a patient will experience adverse drug reactions or drug interactions rises as a number of medicines are taken concurrently [7]. Because of the insulin release process that is glucose-independent, sulfonylureas have a built-in risk of hypoglycemia. When a co-prescribed drug which inhibits CYP2C9 leads to sulfonylurea metabolism being compromised, unintentional toxicity may result [8].

Therefore, the current study's objective is to ascertain whether anti-arrhythmic medications like amiodarone and hypoglycemia drugs like glimepiride interfere with each other in rats that are both healthy and diabetic. The fundamental boundaries examined for the interaction between the aforementioned medications are the impact of amiodarone on glimepiride at the onset, duration, and peak of hypoglycemia. Further investigation is necessary to ascertain whether glimepiride and amiodarone interact.

2. MATERIALS AND METHODS

The Pharmacology department at Dhule Charitable Society's Annasaheb Ramesh Ajmera College of Pharmacy, located at Nagaon, Dhule-424006, Maharashtra, was the location of the research. The department holds dual licences from the CPCSEA and is registered under the number 1367/PO/Re/S/10/CPCSEA. The Institution Animal Ethics Committee (IAEC) has approved the research protocol with the number ARACOP/IAEC0/20/5 in accordance with the CPCSEA's current regulations during its session.

2.1 Animals

For this study, we employed twelve rats of both genders that were purchased from the LACSMI BioFarms in Ale Phata, Pune, Maharashtra. (1277/PO/RcBt/S/09/CPCSEA) is the registration number.

2.2 Drug Administration Methods

The route of drug administration was oral hence an oral feeding needle and a glass syringe were used [9].

2.3 Technique for Drawing Blood

To induce sleep, sedative ether was administered to them in a sedative chamber. The

Fig. 1. Photograph of oral administration of drug using oral feeding needle and syringe.

Fig. 2. Photograph of blood withdrawal from the tail vein of the rat

tail vein is expanded by gently massaging it, and with the use of xylene, its tip is cut off. Blood is subsequently drawn in Eppendorf tube containing an anticoagulant [10-12].

2.4 Calculating Blood Glucose Levels

Since the GOD/POD method is among the most precise, user-friendly, sequential, rapid, reliable, and accepted, it was used [13,14].

3. EXPERIMENTAL PROCEDURE

3.1 Healthy Albino Rats

In this experiment, six rats weighing 150–180 grams each were employed. Their markings made it simple to trace them. Colony cages were used to house the animals in accordance with industry regulations. The food was taken away eighteen hours prior to the experiment beginning on the day before it was scheduled to begin. On the other hand, water was provided without restriction. For the whole experiment, the subjects were fasting. To ensure the baseline amount of glucose was maintained, a further blood sample was drawn from every rat's tail vein for analysis. The animals were then given glimepiride 0.41 mg/kg in a 2% gum acacia suspension orally during the first phase of the trial. Blood was taken from the tail vein at 0, 0.5, 1, 2, 4, 6, 8, 12, 18, and 24 hours, and the GOD/POD procedure was used to analyse the sample. The same group of animals were employed in the second part of the investigation, which took place after an appropriate washout period. The rats received amiodarone at a dose of 50 mg/kg in a 2% gum acacia suspension for seven consecutive days, after which they were fasted on the seventh day. Until all of the results were in, the fast was maintained. On the seventh day, the animals were given glimepiride 0.41 mg/kg, an hour after they had been given amiodarone 50 mg/kg. At the aforementioned periods, blood samples are drawn and examined to ascertain the glucose levels.

3.2 Diabetic Rat

When amiodarone is administered to rats, it remains unclear how effective anti-diabetic medications are in pathological conditions like diabetes. The current study will employ diabetic rats as test subjects to demonstrate this viewpoint.

3.3 Induction of Diabetes

Diabetes was introduced in rats of both sexes. First, 100 mg/kg of freshly made alloxan monohydrate was administered intraperitoneally. The next day, 50 mg/kg of body weight was administered. Subsequently, 10% dextrose was given to avoid hypoglycemia immediately. Rats having fasting blood glucose levels higher than 250 mg/dL were classified as diabetic rats and involved in the study [15,16].

3.4 Experimental Procedure

When estimating blood glucose concentration in diabetic rats, the same method used in healthy rats is applied.

3.5 Statistical Analysis

The "t-test" was employed to evaluate the data. P values of less than 0.05 were used to establish the statistically significant threshold.

4. RESULTS

The parameters considered for the evaluation of influence on glimepiride-induced hypoglycaemia were the onset of hypoglycaemia (time taken by a drug to decrease blood glucose level to the extent of 15% - 20%), duration of hypoglycaemia (time duration in which more than 15% - 20% decrease in blood glucose level is maintained), and peak hypoglycaemia.

4.1 Drug-drug Interaction

The current research is dedicated to exploring the interaction between Amiodarone and Glimepiride, with a particular emphasis on assessing how Amiodarone affects the hypoglycemic response elicited by Glimepiride in healthy and diabetic rats models prior to drug administration.

Table 1. The % of glucose concentration in healthy rats pre and post-amiodarone treatment with glimepiride

Time in hr	Amiodarone group blood glucose concentration (mg/dl)	Glimepiride group blood glucose concentration (mg/dl)	Amiodarone + Glimepiride group blood glucose concentration (mg/dl)
	Mean ± SEM	Mean ± SEM	Mean ± SEM
0	-	-	-
½	1.32±0.11	7.72±0.50	18.98±0.58***
1	2.64±0.08	16.58±0.61	27.89±0.62***
2	3.42±0.12	23.74±0.55	36.14±0.71***
4	4.66±0.29	29.52±0.73	44.18±0.67***
6	5.86±0.21	35.43±0.61	50.68±0.52***
8	7.02±0.09	46.77±0.52	60.67±0.67***
12	5.44±0.21	35.31±0.70	48.88±0.78***
18	3.98±0.15	26.09±0.66	35.79±0.45***
24	2.84±0.19	17.32±0.62	27.14±2.63***

*Mean±SEM; *** Significant at P<0.001; ** Significant at P = 0.01; * Significant at P = 0.05 compared to glimepiride control for n = 6*

Table 2. The % of glucose concentration in diabetic rats pre and post-amiodarone treatment with glimepiride

Time in hr	Amiodarone group blood glucose concentration (mg/dl)	Glimepiride group blood glucose concentration (mg/dl)	Amiodarone + Glimepiride group blood glucose concentration (mg/dl)
	Mean ± SEM	Mean ± SEM	Mean ± SEM
0	-	-	-
½	1.41±0.07	7.13±0.78	20.81±0.78***
1	2.55±0.08	15.98±0.61	28.94±0.69***
2	3.67±0.03	27.07±0.47	37.11±1.13***
4	4.72±0.04	34.12±0.74	44.84±0.71***
6	5.93±0.11	38.32±0.43	50.15±0.74***
8	6.98±0.08	44.50±0.66	60.88±0.62***
12	5.72±0.05	36.18±0.63	48.94±0.39***
18	4.88±0.09	25.89±0.81	36.67±0.92***
24	3.14±0.07	15.97±0.49	28.52±1.21***

*Mean±SEM; *** Significant at P<0.001; ** Significant at P<0.01; * Significant at P< 0.05 compared to glimepiride control for n = 6*

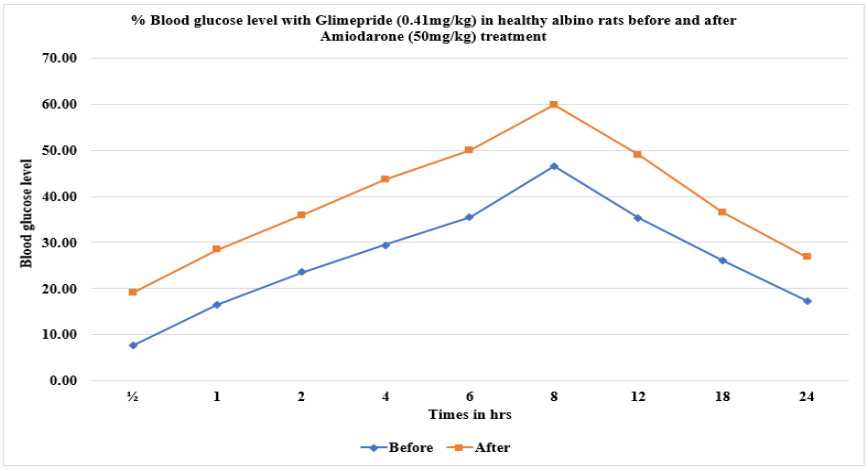

Fig. 3. The % of glucose concentration in healthy rats pre and post-amiodarone treatment with glimepiride

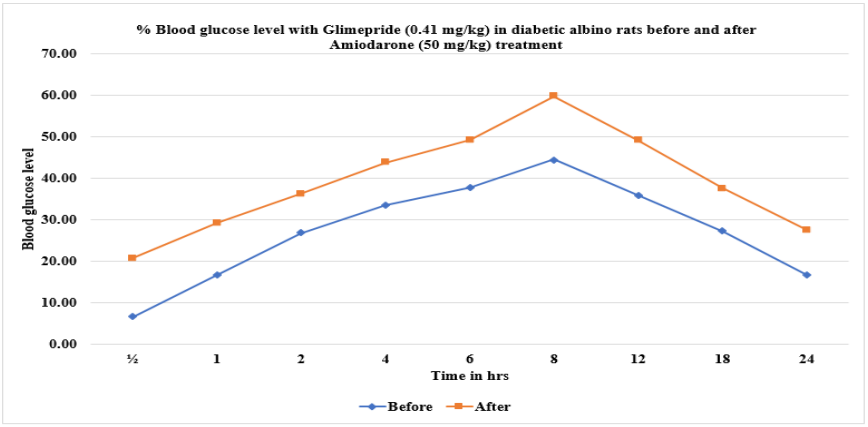

Fig. 4. The % of glucose concentration in diabetic rats pre and post-amiodarone treatment with glimepiride

4.1.1 Pre-drug effect of amiodarone on glimepiride hypoglycemic effect in healthy rats

The onset of hypoglycemia of glimepiride was changed by pre-treatment with amiodarone (from 16.58±0.61% to 27.89±0.62% at 1st hour), peak hypoglycemia was noticeably augmented (from 46.77±0.52% to 60.67±0.67% at 8th hour. Hypoglycemia was continued for 24 hrs (from 17.32±0.62% to 27.14±2.63%) when pre-treatment of amiodarone with glimepiride. Table 1 shows all the results and is also depicted in Fig. 2.

4.2 Effect of pre-Treatment of Amio-darone on the Actions of Glimepiride in Diabetic Rats

In the next stage, the effect of pre-treatment of amiodarone on glimepiride was observed in rats. The onset of hypoglycemia was augmented substantially by pre-treatment with amiodarone (from 15.98±0.61% to 28.94±0.69% at 1st hour), peak hypoglycemia was substantially augmented (from 44.50±0.66% to 60.88±0.62% at the 8th hour). Hypoglycemia persisted for 24 hours (from 15.97±0.49% and increased to 28.52±1.21% post at 24 hours). Table 2 shows all the results and is also depicted in Fig. 3.

5. DISCUSSION

When assessing the efficacy of the hypoglycemic outcome, consideration was given to the onset, extent of time, and peak hypoglycemic consequence (the period that it takes for glucose concentrations to remain at their lowermost stage, or 15%).

Compared to its parent medicine, amiodarone has remained shown to inhibit the

CytochromeP450 enzymes like CYP2D6, 1A2, 2C9, and 3A4 enzymes. This suggests that inhibitory metabolites may get an even additional direct effect [16-19].

These results show that amiodarone alone has not showing direct hypoglycemic effect, suggesting a pharmacokinetic form of drug interaction between glimepiride and amiodarone occur. So, as discussed above amiodarone is a inhibitor of CYP2C9 which is responsible for metabolism of glimepiride resulting into decrease in glimepiride metabolism follow-on potentiation of hypoglycemic activity of glimepiride. In healthy albino rats the amiodarone given for a week, the onset of hypoglycemia with glimepiride was increased i.e., (from 16.58±0.61% to 27.89±0.62% at 1st hour), the duration and peak hypoglycemia were both prolonged i.e., (from 17.32±0.62% to 27.14±2.63%) and (from 46.77±0.52% to 60.67±0.67% at 8th hour respectively. Additionally, when amiodarone and glimepiride were administered for a week before the start of hypoglycemia in diabetic rats, the hypoglycemia's peak and duration increased i.e., (from 44.50±0.66% to 60.88±0.62% at the 8th hour) and (from 15.97±0.49% and increased to 28.52±1.21% post at 24 hours) respectively. Further investigation is necessary to ascertain the effect of amiodarone on glimepiride's pharmacokinetic characteristics in humans.

6. CONCLUSION

According to this study, The inhibition of the CYP2C9 isoenzymes by amiodarone may be responsible for enhancing the hypoglycemic effect of glimepiride in rats when amiodarone and glimepiride both are given together. This information implies that monitoring of blood glucose is required when using glimepiride and amiodarone at the same time. The dosage and schedule of oral antidiabetic medications should be adjusted when amiodarone is taken with them.

Furthermore, the study was carried out on the rats so more human trials are required to confirm this. The study focuses on the inhibition of the CYP2C9 enzyme yet does not explore other pathways that may also be relevant.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts

ETHICAL APPROVAL

The Institution Animal Ethics Committee (IAEC) has approved the research protocol with the number ARACOP/IAEC0/20/5 following the CPCSEA's current regulations during its session.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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