Evaluation of Amiodarone for Its Effect on Glucose Metabolism in Euglycemic Albino Wistar Rats

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Research Article

Abstract: **Objective:** To evaluate the effect of amiodarone on glucose levels in albino wistar rats. **Materials and Methods:** Albino wistar rats were divided in to test group (amiodarone) and control group (distilled water) of six animals each. They were given test drug i.e amiodarone 180mg/kg and distilled water 5ml/ rat respectively for a period of 5 days. On 5th day OGTT (slightly modified) was performed and cbg values were recorded at 0 min, 60min and 150 min respectively. **Results and Discussion:** The cbg values were significantly higher ($p<0.05$) in test group at all the time intervals thereby indicating that amiodarone has hyperglycemic activity in the albino wistar rats. **Conclusion:** Further studies are required to evaluate the effect of amiodarone in humans and it should be used with caution in diabetics patients.

Keywords: amiodarone, Diabetics.

Introduction

Type II DM is at present one of the most challenging health care problems, which requires optimum management. At present the treatment of diabetes mellitus includes insulin, sulfonylureas, biguanides, α-glucosidase inhibitors, DPP-4 inhibitors, thiazolidinediones, GLP-1 receptor agonists, amylin agonists, medical nutrition therapy and lifestyle modification[1]. The International diabetes federation has predicted that the number of diabetics will increase from 240 million in 2007 to 380million by 2025 and that the number of diabetic patients in India are going to be more than doubled from 19 million in 1995 to 40.9 million in 2007 and is projected to increase to 69.9 million by 2025. So India will be the diabetes capital of the world indicating the global population is approaching the midst of diabetes pandemic[2]. Insulin, a hypoglycaemic hormone, is secreted from human pancreas by glucose entry into β cell through GLUT-2. Increased glucose results in inhibition of ATP-sensitive K+channel resulting in depolarisation of β cells. It increases Ca++ entry through voltage sensitive L type calcium channels into the β cells and also releasing Ca++ from intracellular binding sites, such as the internal surface of the cellmembrane, sarcoplasmic reticulum and mitochondria of the β-cell resulting in release of insulin by degranulation of stored vesicles[3]. Many of the drugs used for diseases other than diabetes, interact with receptors. Involved in insulin secretion, causing hypo or hyperglycemia. Hence, they should be evaluated for their effect on blood glucose. Test drug Amiodarone used in the study is a highly lipophilic drug (lop *P*s5.95and p*K*as8.7 at 37.8^{0}C) and is almost insoluble in water or aqueous buffer solution. Amiodarone has long been referred to as a prototype of Class III anti-arrhythmic agents because it was demonstrated in early experimental studies in 1970s that this compound prolongs both APD and the refractory period of cardiac muscle when administered chronically[4]. It exerts multiple actions by blocking delayed rectifier potassium channels, blocks inactivated sodium channels, inhibits calcium channels and has non competitive beta adrenergic blocking property also[5]. With this background amiodarone was evaluated in albino wistar rats for effect on glucose metabolism by its action on calcium and potassium channel blocking activity.

Materials and Methods

Source of data:

Albino rats of either sex of average weight 150-200gms, aged 3-4 months which were bred in central animal house of J.S.S. Medical College, Mysore was selected for the study.

Inclusion Criteria:

- Rats weighing 150-200gms either sex
- Age 3-4 months.
- Healthy with normal behaviour and activity.

Exclusion Criteria:

- Pregnant rats
- Diseased rats

Method of Collection of Data: In this study 12 albino rats (2 groups each containing 6 rats) are used for study. The study group was divided as follows;

1) **Group-1** (**Control**): Distilled water 25ml/kg body wt. (oral)
2) **Group-2** (**Test 1**):amiodarone 180mg/kg body weight(oral)

Instruments used: oral feeding tube, glass beaker, syringes, glucometer, scissor

Models and Methodology of Experiment

Rats were divided into control and test groups to study the effect of glucose induced glycemic changes in normal rats following oral administration of distilled water and amiodarone respectively. The rats were fasted overnight but provided water *ad libitum*. The control group of rats received 25ml/kg of tap water & the test group received amiodarone. Every day in the dose of 180 mg/Kg BW for 5days. On the fifth day, 2 hours after drug administration all the groups of rats were administered oral glucose in the dose of 0.6 gm/Kg BW. The blood glucose levels were measured at 0, 60 and 150minutes after glucose administration (slight modification in OGTT) by rat tail snipping method using ACCUCHEK glucometer[6].

OGTT[7]*:* The oral glucose tolerance test is a measure of the glucose induced insulin secretion mediated glycemic control alteration. This study used OGTT for normal rats with some modifications to the standard method (Duvigneaud and Karr, 1925) to assess the effect of test drugs on glucose induced glycemic alteration. Both the groups of rats were subjected to OGTT.

Results and Discussion

Amiodarone is both calcium and potassium channel blocker; both these channels are indicted in glucose metabolism. Release of insulin requires closure of potassium channels and subsequent opening of calcium channels in beta cells of pancreas.

In the experiment conducted, high basal (0 min) levels of glucose were seen. This is due to blocking of calcium channels which inhibited insulin secretion in absence of any glucose challenge. Test values were almost greater by 22.78%. After 60 minutes of the glucose challenge it was noted the raise of glucose was almost 23.38% when compared to the control values. Due to continued blocking of the calcium channels by amiodarone insulin secretion was prevented leading to high values. 150 minute readings showed a fall in glucose levels when compared to 60 minute reading but the values were high when compared to the control values by almost 16%. This can be probably explained on basis of recruitment of remaining calcium channels for release of insulin. But these values were higher than the control values because of continued action of amiodarone on blocking the calcium channels, though it also blocked the potassium channels.

Table 1: Depicting CBG values of test and control group expressed as mean+/-SEM

Sr. No	Time since administration of glucose in minutes	Mean CBG (mg/dl) +/- SEM		T v/s C (Mg/dl)	% change of CBG of T over C
		Control group (C) (n=6)	Test group (T) (n=6)		
1	0	65.50 +/-1.005	84.83 +/-0.830	T>C	22.78
2	60	83.00 +/-0.781	108.33 +/-0.902	T>C	23.38
3	150	73.67 +/-0.653	87.33 +/-0.902	T>C	15.64

The average 0 minute reading in the test group was 84.83mg% whereas control values were only 65.50mg%. At 60 minute reading in test group average cbg was 108.33mg% whereas it was just 83mg% in control. At 150 minute average difference was relatively lesser between the two groups. Average control reading was 73.67mg% whereas test group recorded 87.33mg%.

Table 2: Depicting difference in CBG values between various time intervals

Sr. No	Time Interval in Minutes	Difference in CBG Values mg/dl	
		Control	Test
1	0-60	17.5	23.5
2	60-150	9.33	21
3	0-150	8.17	2.5

The raise in glucose levels after giving oral glucose was 17.5mg/dl in control group whereas it was 23.5mg/dl in the test group. But a greater fall was noted in the test group between 60 minute reading to 150 minute reading. The 0 and 150 minute reading were almost similar in the test group.

Table 3: Depicting difference in CBG values between various time intervals of test & control respectively

Sr. No.	Time interval between test and control respectively in minutes	Difference in CBG values (mg/dl)
1	0-0	19.33
2	0-60	01.83
3	0-150	11.16
4	60-0	42.83
5	60-60	25.33
6	60-150	34.66
7	150-0	21.83
8	150-60	04.33
9	150-150	13.66

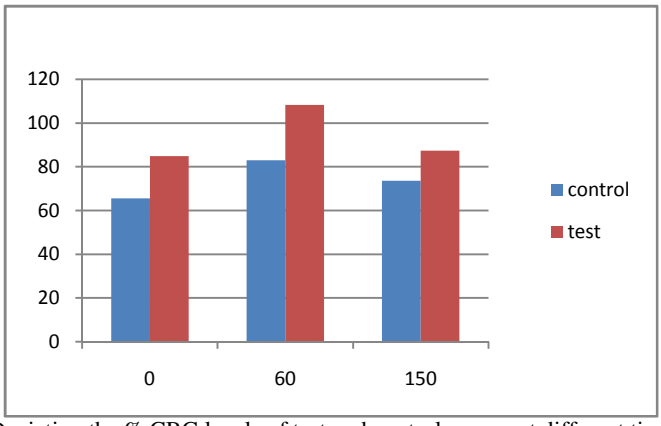

Figure 1: Depicting the % CBG levels of test and control groups at different time intervals

Bar diagram showing the effect of amiodarone on plasma glucose concentration of normal rats in an oral glucose concentration test compared to control at 0, 60 and 150 minutes. Values are mean+/- SEM (n=6). P<0.001 compared to control group where the significance was performed by Oneway ANOVA followed by post hoc Dunnett's test.

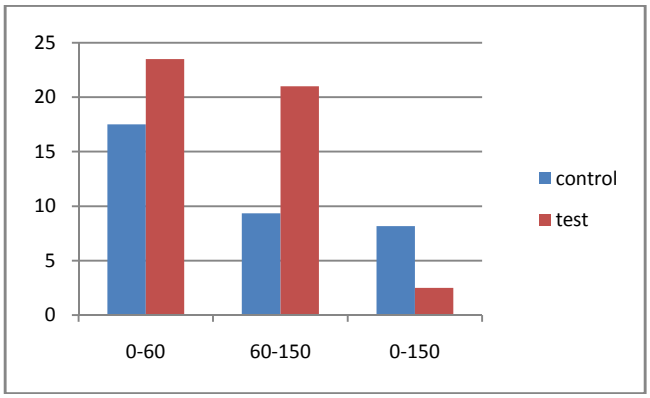

Figure 2: Difference between CBG values of test and control at different time intervals

Bar Diagram showing difference in blood glucose levels between various time intervals of 0-60, 60-150 and 0-150 minutes among control and amiodarone group

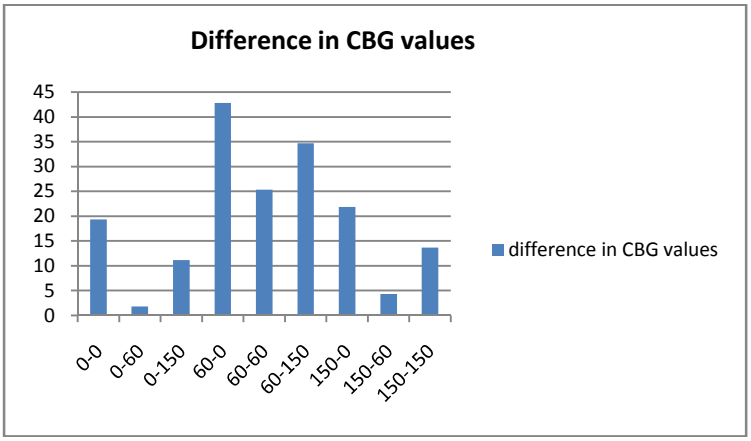

Figure 3: The relationship of CBG values compared at different time intervals of Test and Control and the difference between CBG values of Test and Control

Bar diagram showing difference in plasma glucose levels between various time intervals of test and control groups respectively.

Conclusion

This study has shown hyperglycemic effect of amiodarone in albino wistar rats through glucose challenge. Hence further studies are required to assess effect of amiodarone on glucose levels, as on one hand it has a pro insulin secreting effect by blocking potassium channels but on other hand have a insulin secretion inhibiting effect. The P values showing hyperglycemic

effect were significant at 0minute, 60 minute as well as 150 minute. Also it can be assumed that calcium channels have a predominant role than the potassium channels in secretion of insulin. Amiodarone should be used with caution in diabetic patients.

Acknowledgement

Special thanks to Mr. Mohammed Hibbatullah, Vellore in preparation of Research Article and kind support.

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