



## “A STUDY OF DRUG INTERACTION OF GLIPIZIDE WITH AMIODARONE ON BLOOD GLUCOSE LEVEL IN DIABETIC MICE”

### Pharmacology

**Dr Devendra Singh Doneriya** Associate. Professor, Department of Pharmacology, G. R. Medical College, Gwalior, India.

**Dr Praveen Gautam\*** Associate Professor, Department of Preventive & Social medicine G. R. Medical College, Gwalior, India. \*Corresponding Author

### ABSTRACT

Arrhythmias are co-morbidity found in many patients suffering from diabetes mellitus and amiodarone may be prescribed along with the anti-diabetic agent. Therefore, present work was planned to evaluate drug-drug interaction between amiodarone with glipizide. The study also included evaluation of per se effects of each drug as well as their combinations in alloxan induced diabetic mice. In this work, we evaluated drug interaction of amiodarone (50 mg/kg p.o.), glipizide (2.5 mg/kg p.o.) and combination of glipizide with amiodarone (2.5 + 50 mg/kg, p.o.). The results showed that glipizide reduced blood glucose levels at 2, 3 and 5 hrs period and the difference were statistically significant at 3 and 5 hrs in comparison to control group ( $p < 0.05$ ). The per se showed slight decrease in blood glucose levels which was comparable to the control group ( $p > 0.05$ ). However, statistically significant difference in comparison to glipizide group was observed at 3 and 5 hrs ( $p < 0.05$ ) as the blood glucose reduction was significantly less in comparison to that of the glipizide group. It indicated no acute effect of amiodarone on blood glucose level. However, the combination group (G+A) produces significant increase in blood glucose levels as compared to control group at 3 and 5 hours and results were comparable to that of the glipizide groups. The results showed significant acute variation on blood glucose by amiodarone when given in combination with glipizide. So, the finding of DI of glipizide with amiodarone suggest that acute administration of anti arrhythmic drug did not affected blood glucose level as well as if it is used as combination with anti diabetic drug glipizide.

### KEYWORDS

#### INTRODUCTION –

Day-by-day new medications are continually being introduced to the market and knowledge of drug interactions to clinicians is essential for dealing with the challenging drug interactions; as therapeutic outcome is significantly affected by negative DIs. A drug interaction is considered clinically significant when it occurs between two or more co-administered agents and results in the need for a dosage adjustment of one of the agents or need to use of other alternative

medical intervention [1]. Drug interaction (DI) can be defined as a modification of the effect of a drug when administered with another drug. The effect may be an increase or a decrease in the action/s of either substance, or it may be an adverse effect that is not normally associated with either drug [2]. The particular interaction may be the result of a chemical-physical incompatibility of the two drugs or a change in the rate of absorption or the quantity absorbed in the body, the binding ability of either drug, or an alteration in the ability of receptor sites and cell membranes to bind either drug. Drug Interactions (DIs) are an important cause of drug related problems and this includes significant morbidity and mortality. Epidemiological studies on drug interaction supports that incidence of adverse drug interactions has been estimated to be between 2.2 and 30% in hospitalized patients and between 9.2 and 70.3% in ambulatory patients [3-6]. Drug interactions are important in clinical practice and have been estimated to account for 6-30% of all adverse drug reactions (ADRs) [7]. Diabetes mellitus is endocrinological disorder, which leads to hyperglycemia. The World Health Organization projects that by the year 2025 more than 5% of the world population, i.e. 300 million people will suffer from diabetes. arrhythmias are co-morbidity found in many patients suffering from diabetes mellitus and amiodarone may be prescribed along with the anti-diabetic agent. therefore, present work was planned to evaluate drug-drug interaction between amiodarone with glipizide. The study also included evaluation of per se effects of each drug as well as their combinations in alloxan induced diabetic mice.

#### AIMS & OBJECTIVES

- To evaluate, whether oral antiarrhythmic drug- amiodarone affect blood glucose level in diabetic mice i.e. per se effect of amiodarone on blood glucose level.
- To assess any acute change in blood glucose level has been observed on administration of oral antiarrhythmic drug- amiodarone in combination with glipizide in diabetic mice.

**Material & Methods** – This study was conducted on swiss albino mice in the department of pharmacology at MGM Medical College, Indore, MP.

#### Animals-

Swiss albino mice of either sex were used for the experiments

#### Drugs-

Alloxan (Power Alloxan Monohydrate, Suvidhinath, India)  
Amiodarone (Tab. Tachyra, CIPLA LTD. MALPUR, Dist. Solan INDIA)

Glipizide (Tab. Glynase, USV limited, India)  
Gum Acacia (Himedia laboratories)

#### Equipments/ Instruments

- Glucometer – Accu Check Active: Made in Ireland.
- Singal Pan Electronic Analytical balance A&D, JAPAN
- Electronic weighing machine
- Mice holder
- Tuberculin syringes (1 ml)
- Needles (22, 23, 24 G)
- Feeding needle (16 G)
- Oral gavages
- Test tubes, beakers, flasks
- Glass mortar pestle
- Surgical hand gloves and Spirit.

**Ethical approval** – This study project was submitted for approval to the Institutional Animal Ethics committee (IAEC) of our institution – M.G.M. Medical College, Indore (Reg. NO. 709).

#### Methodology

##### 1. Method for oral administration of drug :

A 16 or 18 gauge needle was suitably covered with flexible polythene tubing, where the edge was made blunt, the needle was fixed to 1ml tuberculin syringe. the mice was held firmly in left hand, the needle was moistened with glycerin and inserted right in to the esophagus and gently pressing plunger for drug administration, and this was followed by 0.2ml of distilled water to ensure administration of correct dose of drug.

- Induction of diabetes in mice: Using alloxane [8,9,10] Procedure: Swiss albino mice (20-30 g) were procured from our central animal

house. They were kept under standard environmental conditions of temperature, relative humidity and were fed with standardized diet and water ad libitum during an acclimatization period. The mice were fasted for 18 hours before experimentation but were allowed free access to water. Diabetes was induced by the injection of 150 mg/kg (i.p.) of fresh prepare alloxan monohydrate soluble in water for injection immediately before use. Seventy-two hours later, the fasting blood glucose level in the mice was determined [11], the blood glucose levels these animals were measured through tail clipping method using a one touch Glucometer device with strips [12]. In this method the mouse was held in a mild restraining device and the distal 1 to 2 mm of the tail was clipped using a sterilized razor [13] and the droplet of blood collected directly on the glucometer strip. Only one droplet was sufficient for blood glucose determination on each occasion. Diabetes was further confirmed after 8 days and animals with fasting blood glucose of 250-350 mg % were considered appropriate and were used in the study [14,15]

**3 Preparation of drugs for animal experimentation:**

The suspension of Glipizide , amiodarone and solutions of both to be given orally to the experimental animals as standard or in combination, were prepared in 2% gum acacia. Gum acacia here acted as a vehicle. Control group was given a 2% gum acacia suspension (in the standard dose of 10 ml/kg) orally. For all the studies 6 animals were kept in each group (n=6).

**Drug Interaction study**

To estimate and demonstrate change in blood glucose level on administration of Glipizide with amiodarone using oral route in diabetic mice:

A single dose study employing serial sampling of blood was used as mentioned above.

**Animals:** Albino mice; Swiss strain (20-30 gm)

**Groups-**

**CON.** - Control Group I; (2% gam acacia)

**GLP.** - Glipizide Group II; (2.5mg/kg BW)

**AM.** - Amiodarone Group III; (50 mg/kg BW)

**G+D.** - Glipizide + Amiodarone Group IV; combination; (2.5mg/kg+ 50 mg/kg BW respectively)

**Procedure:**

Alloxan induced diabetic albino mice were selected for the study by following the procedure mentioned above. Each animal was weighed and individual doses (volume of drug solution to be given) were calculated. Random blood glucose levels (pre dose, 0 hr) were measured in the morning, on the day of the experiment. Then drugs were administered orally to all groups at the stipulated doses and the time of dosing was noted for all the animals in each group. Blood glucose levels were measured in all the animals at 0, 2, 3 and 5 hrs respectively after dosing.

**OBSERVATIONS & RESULTS –**

**Table D -1: Statistical analysis of effect of drugs on Blood Glucose Level in alloxane- induced diabetic mice.**

| Drug treatment (dose (p.o.) BW) | Blood Glucose level mg% ± SEM |                |                |              |      |
|---------------------------------|-------------------------------|----------------|----------------|--------------|------|
|                                 | 0hr                           | 2hr            | 3hr            | 5hr          |      |
| CON-                            | 256 ± 16.37                   | 227.33 ± 17.00 | 220.66 ± 14.01 | 221.33±10.69 |      |
| GLP                             | 252.33 ± 7.37                 | 216.33 ± 1.15  | 215.33 ± 14.97 | 211.33±11.93 |      |
| AM                              | 252.33 ± 7.76                 | 241.33 ± 26.68 | 222 ± 22.64    | 208 ± 13.07  |      |
| G+AM                            | 332.33 ± 84.61                | 336.66 ± 173.5 | 274.66± 71.30  | 228 ± 13.89  |      |
| One-way ANOVA                   | F                             | 2.47           | 1.17           | 1.54         | 1.62 |
|                                 | Df                            | 3              | 3              | 3            | 3    |
|                                 | p                             | <0.5           | <0.5           | <0.5         | <0.5 |

CON- Control, GLP- Glipizide, AM- Amiodarone, G+AM-

Glipizide-Amiodarone combination, Values are mean ± SEM, n=6 in each group,\*

p<0.05 compared with control, # p<0.05 Compared with GLP and @ p<0.05 compared with amiodarone, # p<0.05, (Tukey's test)

**Inference –**

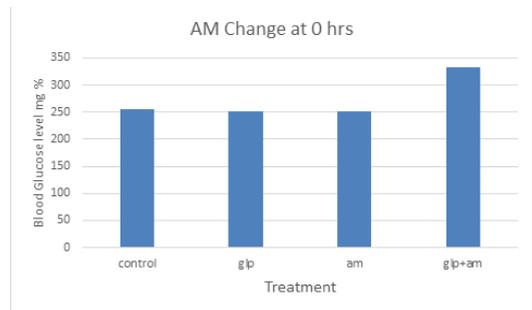
Glipizide showed depletion in blood glucose levels at 2, 3 and 5 hrs period and the difference were statistically significant at 3 and 5 hrs in comparison to control group (p<0.05).

The amiodarone group, though showed slight increase in blood glucose levels at 2, 3 and 5 hrs., the increase was not statistically significant as compared to control group (p>0.05). However, it

showed statistically significant difference in comparison to glipizide group at 3 and 5 hrs. (p<0.05), since blood glucose reduction was significantly less in comparison to lowering of blood glucose by glipizide group.

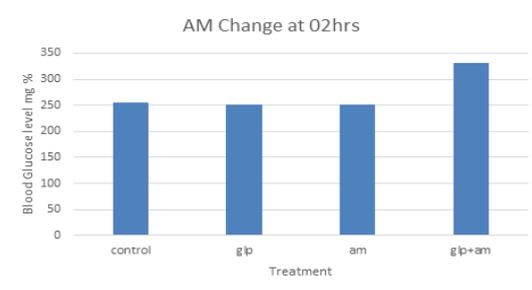
The combination group (G+D) also produces significant increase in blood glucose levels as compared to control group at 3 and 5 hours. Though effect of combination was more significantly different as compared to glipizide group (p<0.05) at all time period. Yet, it showed significant difference in comparison to amiodarone group (p<0.05).

**Graphs: AM-1 Change in Blood Glucose Level at 0 hrs. in diabetic mice**



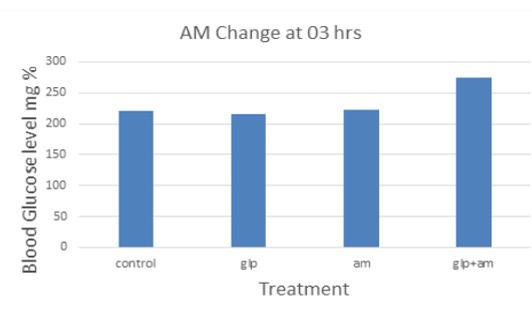
CON- Control, GLP- Glipizide, AM- Amiodarone, G+AM- Glipizide- Amiodarone combination

**Graphs: AM-1.1 Change in Blood Glucose Level at 2 hrs. in diabetic mice**

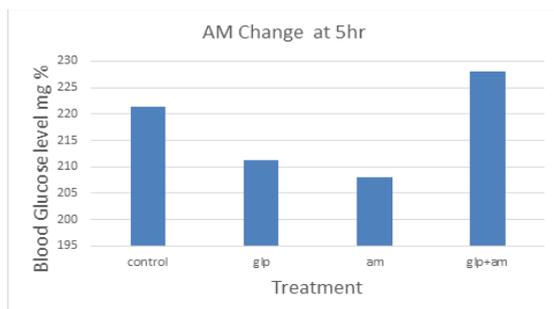


CON- Control, GLP- Glipizide, AM- Amiodarone, G+AM- Glipizide- Amiodarone combination

**Graphs: AM-1.2- Change in Blood Glucose Level at 3 hrs. in diabetic mice**



### Graphs AM 1.3 Change in blood glucose level at 5hrs in diabetic mice



#### ORIGINAL RESEARCH

#### DISCUSSION & CONCLUSION –

Drug-drug interaction of glipizide with Amiodarone -

In this work, we evaluated drug interaction of Amiodarone (50 mg/kg p.o.), glipizide (2.5 mg/kg p.o.) and combination of glipizide with Amiodarone (2.5 + 50 mg/kg, p.o.). Amiodarone is an antiarrhythmic medication used to treat and prevent a number of types of irregular heartbeats. [16] This includes ventricular tachycardia (VT), ventricular fibrillation (VF), and wide complex tachycardia, as well as atrial fibrillation and paroxysmal supraventricular tachycardia. [16]

The results showed that glipizide increase blood glucose levels at 2, 3 and 5 hrs period and the difference were statistically significant at 3 and 5 hrs in comparison to control group ( $p < 0.05$ ), (table D-1 and graphs D-1 to D-1.3). This action is produced by blocking potassium channels in the beta cells of the islets of Langerhans. [17]

The amiodarone showed increase in blood glucose levels which was comparable to the control group ( $p > 0.05$ ). However, statistically significant difference in comparison to glipizide group was observed at 3 and 5 hrs ( $p < 0.05$ ) as the blood glucose reduction was significantly more in comparison to that of the glipizide group. It indicated no acute effect of Amiodarone on blood glucose level. However, the combination group (G+Am) produces more significant increase in blood glucose levels as compared to control group at 3 and 5 hours and results were comparable to that of the glipizide groups. The results showed more significant acute variation on blood glucose by Amiodarone when given in combination with glipizide. Probable chronic administration of Amiodarone may affect blood glucose level that needs to be explored.

So, the finding of DI of glipizide with Amiodarone suggest that acute or very common used for the chronic treatment many arrhythmias drug Amiodarone per se did not affect blood glucose level as well as if it is used as combination with antidiabetic drug glipizide. Though, because of pharmacokinetic and pharmacodynamic variation between animals and human species further studies are required to confirm these results in human diabetic subjects.

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