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"The study of drug interaction of Glipizide with Dapsone on blood glucose level in diabetic mice"

KEYWORDS

Dr. Devendra singh Doneriya
Assist. Professor, Pharmacology, G. R. Medical College, Gwalior, India.

Dr. Savita Vyas
Associate Prof. Pharmacology, MGM Medical College, Indore, India.

ABSTRACT *Infections are common co-morbidity found in many patients suffering from diabetis mellitus and dapsone may be prescribed along with the anti-diabetic agent. Therefore, present work was planned to evaluate drug-drug interaction between dapsone 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 dapsone (50 mg/kg p.o.), glipizide (2.5 mg/kg p.o.) and combination of glipizide with dapsone (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 dapsone 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 dapsone on blood glucose level. However, the combination group (G+D) produces significant decrease 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 no significant acute variation on blood glucose by dapsone when given in combination with glipizide. So, the finding of DI of glipizide with dapsone suggest that acute administration of anti leprosy drug dapsone per se did not affect blood glucose level as well as if it is used as combination with anti diabetic drug glipizide.

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.

infections are common co-morbidity found in many patients suffering from diabetis mellitus and dapsone may be prescribed along with the anti-diabetic agent.

Therefore, present work was planned to evaluate drug-drug interaction between dapsone 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

1. To evaluate, whether oral anti-leprosy drug (dapsone) affect blood glucose level in diabetic mice i.e. per se effect of dapsone on blood glucose level.
2. To asses any acute change in blood glucose level has been observed on administration of oral anti-leprosy drug (dapsone) 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)
Dapsone (Tab.Dapsone, (GlaxoSmithKline Pharmaceutical Limited, 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 –

The 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

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followed by 0.2ml of distilled water to ensure administration of correct dose of drug.

2. 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 , Dapsone 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 Dapsone 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)

DPS.- Dapsone Group III; (50 mg/kg BW)

G+D. - Glipizide + Dapsone 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.

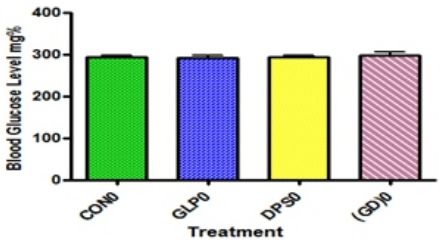
Drug Treatment (Dose (p.o.) BW)	Blood Glucose Level mg% ± SEM			
	0 hr	2 hr	3hr	5hr
CON (2 % Gum acacia)	292.3 ± 5.469	281.5 ± 6.048	271.7 ± 4.883	259.7 ± 5.220
GLP (2.5 mg/kg)	290.8 ± 6.775	269.5 ± 5.743	243.2 ± 4.293*	229.2 ± 4.983*
DPS (50 mg/kg)	292.8 ± 4.393	279.8 ± 4.629	268.5 ± 4.485#	260 ± 5.36#
G + D (2.5 + 50 mg/kg)	297.2 ± 8.573	273 ± 9.564	243.5 ± 7.338*@	231 ± 11.2*@
One-way ANOVA	F 0.176	0.703	8.266	5.813
	Df 3,20	3,20	3,20	3,20
	p >0.05	>0.05	>0.001	<0.001

CON- Control, GLP- Glipizide, DPS- Dapsone, G+D- Glypizide-Dapsone 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 dapsone, # p<0.05, (Tukey's test)

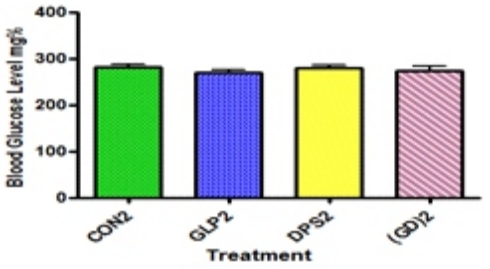
Inference –

- 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 dapsone group, though showed slight decrease in blood glucose levels at 2, 3 and 5 hrs., the decrease 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 decrease in blood glucose levels as compared to control group at 3 and 5 hours. Though effect of combination was not significantly different as compared to glipizide group (p<0.05) at all time period. Yet, it showed significant difference in comparison to dapsone group (p<0.05).

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

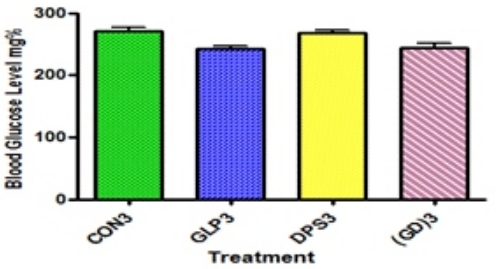


Graphs: D-1.1 Change in Blood Glucose Level at 2 hrs. in diabetic mice



CON- Control, GLP- Glipizide, DPS- Dapsone, G+D- Glypizide-Dapsone combination

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



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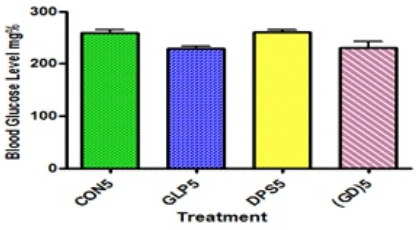
Graphs: D-1.3 Change in Blood Glucose Level at 5 hrs. in diabetic mice



CON- Control, GLP- Glipizide, DPS- Dapsone, G+D- Glypizide-Dapsone combination

Table D-2 :Percentage change in Blood Glucose Levels from fasting (0hr) in diabetic mice.

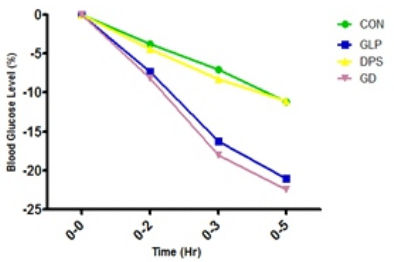
Treatment (Dose(p.o.) BW)	Percentage change in Blood Glucose Levels from fasting % ± SEM			
	0hr	0-2hr	0-3hr	0-5 hr
CON (2 % Gum acacia)	0	-3.722 ± 0.598	-7.045 ± 0.791	-11.146 ± 1.18
GLP (2.5 mg/kg)	0	-7.286 ± 1.068	-16.273 ± 1.468	-21.058 ± 2.035
DPS (50 mg/kg)	0	-4.441 ± 0.626	-8.285 ± 1.152	-11.128 ± 0.735
G + D (2.5 + 50 mg/kg)	0	-8.160 ± 1.369	-18.004 ± 1.446	-22.471 ± 2.049

CON- Control, GLP- Glipizide, DPS- Dapsone, G+D- Glypizide-Dapsone combination

Inference-

All the groups showed varying percentage of decreased in blood glucose levels. Glipizide and combination groups showed sharp decrease in blood glucose level as compared to other groups. Combination group G+ D follow similar pattern for reduction of blood glucose as that of the glipizide when given alone. Thus, indicating no significant change in effect of glipizide when given in combination with dapsone.

Graph D-2 : Effect of drugs on percent change in blood glucose levels in 5 hours



CON- Control, GLP- Glipizide, DPS- Dapsone, G+D- Glipizide-Dapsone combination

DISSCUSSION & CONCLUSION –

Drug-drug interaction of glipizide with dapsone -

In this work, we evaluated drug interaction of dapsone (50 mg/kg p.o.), glipizide (2.5 mg/kg p.o.) and combination of glipizide with dapsone (2.5 + 50 mg/kg, p.o.). Dapsone (diamino-diphenyl sulfone) is an antibacterial most commonly used in combination with rifampicin and clofazimine as multidrug therapy (MDT) for the treatment of Mycobacterium leprae infections (leprosy). 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 ($p < 0.05$), (table D-1 and graphs D-1 to D-1.3). The action is produced by blocking potassium channels in the beta cells of the islets of Langerhans. [16]

The dapsone 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 dapsone on blood glucose level. However, the combination group (G+D) produces significant decrease 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 no significant acute variation on blood glucose by dapsone when given in combination with glipizide. Ying-Chuen Lai et al. has reported that dapsone may be the cause of artificially low HbA1c and suggested to monitor glycemic control when dapsone is used for the treatment of concurrent disordersm **[17].** In an another study, unexpectedly low HbA1c levels in two diabetes patients following dapsone use has been reported by Unnikrishnan et al**[18].** Variation in HbA1c is an indication of uncontrolled blood glucose levels. We were therefore interested to explore acute effect of dapsone on blood glucose level if any. Probable chronic administration of dapsone may affect blood glucose level that needs to be explored.

So, the finding of DI of glipizide with dapsone suggest that acute administration of anti leprosy drug dapsone *per se* did not affect blood glucose level as well as if it is used as combination with anti diabetic 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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