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Effect of Ofloxacin and Glibenclamide Co-Administration on the Blood Glucose Level in Normal Wistar Rats

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ABSTRACT

Drug-drug interaction (DDI) is one of the major problems in multi-drug therapy. Patients suffering from diabetes mellitus are prone to urinary tract infection in such cases sulfonylurea and fluoroquinolone are administered simultaneously. There is a possibility of occurrence of DDI when Ofloxacin (commonly used fluoroquinolone) and Glibenclamide (commonly used sulfonylurea) are concomitantly used. Therefore, the present study was carried out to ascertain the possibility of such interaction on plasma glucose levels in normal wistar rats. The rats were divided into 4 groups and administered; Group- I (Normal Control), Group-II (Glibenclamide-0.45mg/kg), Group-III (Ofloxacin-3.33mg) and Group-IV (Ofloxacin-3.33mg/kg & Glibenclamide-0.45mg). Fasting blood samples were collected at 0, 2, 4, 5 and 8 hrs and blood glucose level was analyzed. The effect of Glibenclamide (0.45mg/kg) and Ofloxacin (3.33mg/kg) on fasting blood glucose (FBG) level was significantly decreased by 33.89% on first day at 5th hour of drug administration. Similarly, on 8th day the FBG level was decreased by 44.42% at 5th hour of drug administration. This indicate that Ofloxacin influence on pharmacodynamics properties of Glibenclamide as the intensity of hypoglycaemia induced by Glibenclamide is enhanced with multiple dose Ofloxacin. The exact mechanism of interaction is not known and probable mechanism may be due to enhance insulin secretion by Ofloxacin treatment that may cause hypoglycemia. Therefore, blood glucose level should be monitored closely and the dose of Glibenclamide needed to be adjusted during initiation and discontinuation of Ofloxacin.

INTRODUCTION

Drug-drug interaction (DDI) is one of the major problems in multi-drug therapy. It is defined as the modification of the effects of one drug (i.e. the object drug) by the prior or concomitant administration of another drug *(Parameshappa, 2002).* DDI can be desired or result in adverse effects like reduced effectiveness or increased toxicity of the drugs involved *(Becker, Kallewaard et al., 2005).* Multiple drug therapy is a common practice to treat chronic disorders like diabetes mellitus where one drug may interact with other drug leading to DDI *(Kumar, Raghu Ram et al., 2008).*

There is an increased rate of infections associated with Type 2 diabetes, with urinary tract infections (UTI) among the most commonly encountered. Over the 1-year follow-up period, 46.9% UTI events were observed among diabetes patients and 29.9% UTI events were observed among patients without diabetes (*Hirji, Guo et al., 2010).* Patients suffering from diabetes mellitus typically old age/ middle age that are prone to urinary tract infection in such cases sulfonylurea and fluoroquinolone are administered simultaneously. There is a possibility of occurrence of DDI when ofloxacin (fluoroquinolone) and glibenclamide (sulfonylurea) are concomitantly used. Therefore, the present study was carried out to ascertain the possibility of such interaction on plasma glucose levels in animal models.

MATERIALS AND METHODS

Selection of Animal Species

Wistar Rats of either sex weighing between 120-180 g were selected and animals were maintained under uniform laboratory conditions (12 h light and 12 h dark cycle) with room temperature (37ºC) and Relative Humidity (RH) 40-60%. The animals were fasted for 18 hour prior to experimentation but allowed free access to water. The animal study was permitted by the Institutional Animal Ethics Committee and bearing IAEC No.- HPI/2018/60/IAEC/PP-0160.

Study Design

The rats were divided into 4 groups of 8 each.

Group- I (Normal Control: Normal diet, n=8)

Group-II (Glibenclamide -0.45mg/kg per oral, n=8)

Group-III (Ofloxacin-3.33mg/kg per oral, n=8)

Group-IV (Ofloxacin-3.33mg/kg + Glibenclamide -0.45mg/kg per oral, n=8)

Experimental Protocol

Single dose interaction study

Procedure

Wistar Rats of either sex weighing between 120-180 g marked suitably were selected for the study and were fasted for 18 hrs before commencing the experiment. During this period, the rats were allowed to take sufficient amount of water. Fasting was continued till the completion of the experiment. The "0" hour blood sample were collected for fasting blood glucose levels estimation. Then Group II animals were administered Glibenclamide (0.45 mg/kg) orally, Group III animals were administered Ofloxacin (3.33mg/kg), Group IV were administered 3.33mg/kg Ofloxacin initially followed by 0.45 mg/kg glibenclamide after 10 minutes and the blood samples were collected at 2, 4, 5 and 8 hrs and blood glucose level was analyzed.

As, Glibenclamide and Ofloxacin practically insoluble in water, so ethanol is used as the co-solvent.

Multiple dose interaction study

The multiple dose interaction study in normal rats were performed with animals of group IV that were administered with Ofloxacin 3.33 mg/kg for the following 7 consecutive days, post single dose interaction. During this period, the animals had free access to food and water. On the 7^{th} day, 8 hr. post Ofloxacin administrations; the animals were deprived of food and had access to sufficient amount of water. On day 8, half an hour after administration of Ofloxacin 3.33 mg/kg the animals were administered with Glibenclamide 0.45 mg/kg. The blood samples were collected at 2, 4, 5 and 8 hours by tail vein puncture and the blood glucose levels were estimated using Glucometer. (Accu-check)

Glucose reduction calculations

Percentage Reduction in Blood Glucose Level (BGL)= {(IBGL – FBGL)/ IBGL}×100 where IBGL = initial blood glucose level; FBGL = final blood glucose level.

Statistical analysis

All statistical analyses were performed using PRISM software. All values were presented as means ± S.D. (standard deviation). Comparisons among groups were made by application of two-way analysis of variance ANOVA followed by Bonferroni test. Differences were considered statistically significant if $p<0.05$, $p<0.01$ and $p<0.001$.

RESULTS

Effect of single dose Glibenclamide and pretreatment with Ofloxacin on fasting blood glucose levels in normal wistar Rats

In this experiment, onset of hypoglycemia (time taken to reduce the blood-glucose level to the extent of 15%) and duration of hypoglycemia (time duration in which a minimum of 15% reduction in blood-glucose levels is maintained) were the parameters considered to evaluate the possibility of drug-drug interaction between glibenclamide and ofloxacin.

The effect of Glibenclamide (0.45mg/kg) and Ofloxacin (3.33mg/kg) on fasting blood glucose (FBG) level is significantly decreased compared to control group with percentage reduction in FBG level (8.47% to 33.89%) compare to control group at 5th hour of drug administration.

The results of these findings are compiled in table no. 1 and fig.1.

Table 1: Mean blood glucose levels (mg/dl) at different time intervals on same day

Time (hr.)	Mean blood glucose levels (mg/dl)			
	Control	Glibenclamide	Ofloxacin	Glib.+ Oflox.
0	67.25±8.31	59.375±8.15	58.25±6.96	65.375±7.65
2	69±7.76	48.75±7.34***	53.75±7.04***	58±5.31*
4	62.75±8.41	42±7.01***	52.62±7.2	51.12±8.98*
5	61.12±4.99	39±6.07***	55.5±9.84	35.75±5.62***
8	61±8.22	54.37±7.55	51.25±11.74	49.5±6.04

Data expressed as Mean ±SD (n=8) followed by Two way ANOVA (Bonferroni test) *P<0.05,**P<0.01,***P<0.001 when Control group compared with Glibenclamide treated, Ofloxacin treated, Ofloxacin+Glibenclamide treated group.

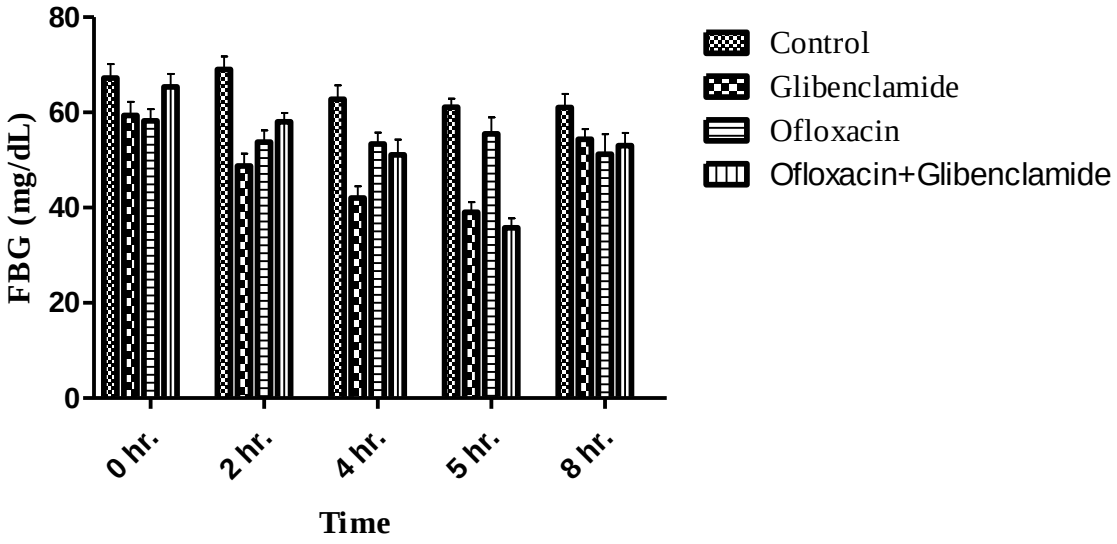

Figure 1: Mean blood glucose levels at different time intervals on various treatments

Table 2: Percentage reduction in blood glucose levels on various treatments

Time (hr.)	Percentage reduction in blood glucose levels			
	Control	Glibenclamide	Ofloxacin	Glib.+ Oflox.
2	2.88	18.01	7.77	10.79
4	6.7	29.49	8.38	22.19
5	8.47	27.32	10.54	33.89
8	5.09	11	6.76	23.47

Effect of multiple dose glibenclamide and ofloxacin treatments on fasting blood glucose levels in normal wistar rats

In this experiment, Group III animals were treated with Ofloxacin (3.33mg/kg) consecutively for a week. Then on 8th day Ofloxacin (3.33 mg/kg) followed by Glibenclamide (0.45 mg/kg) was administered. Then the fasting blood glucose level was monitored to evaluate the possibility of drug-drug interaction between multiple dose of Ofloxacin in presence of Glibenclamide.

The effect of Glibenclamide (0.45mg/kg) + Ofloxacin (3.33mg/kg) on fasting blood glucose (FBG) level on 8th day was significantly decreased compared to control group with percentage reduction in FBG level (8.47% to 44.42%) compare to control group at 5th hour of drug administration.

The results of these findings are compiled in table 3 & 4 and fig. 2.

Table 3: Mean blood glucose levels in multiple dose Ofloxacin in presence of Glibenclamide

Mean blood glucose levels		
Control	Glibenclamide	Multiple dose
67.25±8.31	59.375±8.15	67.62±6.32
69±7.76	48.75±7.34***	54.5±6.11***
62.75±8.41	42±7.01***	49.5±6.23***
61.125±4.99	39±6.07***	30.5±5.83***
61±8.22	54.37±7.55	45.12±5.59***

Data expressed as Mean ±SD (n=8) followed by Two way ANOVA (Bonferroni test) (n=8).*P<0.05,**P<0.01,***P<0.001 when Control group compared with Ofloxacin+ Glibenclamide multiple dose treated group.

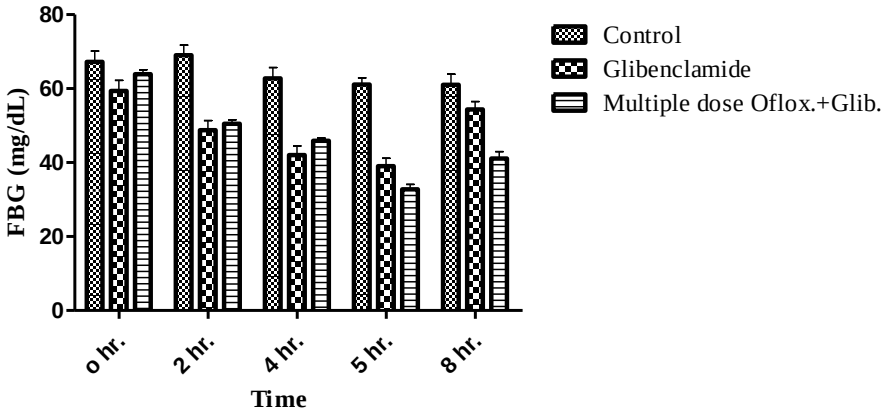

Fig. 2: Mean blood glucose levels in multiple dose of Ofloxacin in presence of Glibenclamide treatment

Table 4: %reduction in blood glucose levels

Time (hr.)	Percentage reduction in blood glucose levels		
	Control	Glibenclamide	Ofloxacin+ Glibenclamide
2	2.88	18.01	19.41
4	6.7	29.49	26.81
5	8.47	27.32	44.42
8	5.09	11	28.31

DISCUSSION

Glibenclamide is a potent second generation sulfonylurea which has been widely used in the management of type II diabetic mellitus in Europe since 1969 and in United States since 1984 (also known as "glyburide") *(Coppack, Lant et al. 1990)*. The mechanism of action of glibenclamide comprises of inhibition of the ATP sensitive K + channel and improve glucose tolerance mainly by augmenting insulin secretion (*Inzucchi 2002).*

Ofloxacin is a second-generation bactericidal broad-spectrum oral fluoroquinolone. It primarily effect by the inhibition of bacterial DNA gyrase (topoisomerase II) which in turn inhibits DNA replication and transcription, DNA repair, recombination and transposition, causing bacterial cell death. It possesses high antibacterial activity against both Gram-positive and Gram-negative bacteria including *Pseudomonas* with indications including upper and lower respiratory tract infections, genito-urinary tract infections as well as skin and soft tissue infections (*Verho, Malerczyk et al. 1986)*.

Recently in July 2018, US-FDA have warned for tight control on blood glucose monitoring when fluoroquinolones are used in diabetics under sulphonylurea due to reporting of hypoglycaemic events. So, it is necessary to realize a clinical study to evaluate the possible alteration of the hypoglycemic effect when Glibenclamide co-administered with Ofloxacin.

In the present study, the possible interactions between the two different classes of drugs used to treat two different pathophysiological conditions like diabetes mellitus and urinary tract infections/ other infections are investigated. The patients suffering from diabetes mellitus typically old age/middle age that are prone to be infected with various pathogens, in such cases sulfonylurea and fluoroquinolone are needed to be administered simultaneously.

From the present investigation it was observed that Glibenclamide (0.45mg/kg) in presence of Ofloxacin (3.33 mg/kg) increase the hypoglycemia. Activity of Glibenclamide was significantly altered on concomitant use of ofloxacin at 5 hour interval on single dose as well as multiple dose treatment of Ofloxacin.

Our result has indicated that Ofloxacin influence on pharmacodynamics properties of Glibenclamide. Since the intensity of hypoglycaemia induced by Glibenclamide are enhanced, it can be concluded that Ofloxacin appear to interfere with the pharmacodynamics profile of Glibenclamide.

According to *maiden 2018,* fluoroquinolones are able to enhance insulin secretion and the hypoglycemic risk is higher in patients taking fluoroquinolones and sulfonylureas together. It could be the possible mechanism for the pharmacodynamics interaction of Ofloxacin and Glibenclamide.

The study by *ghaly 2009* showed that ATP sensitive K + channel blocking effect is a condition for the hypoglycemic side effect of the fluoroquinolones and the use of Glibenclamide (inhibit ATP sensitive K + channel) augment the hypoglycaemic effect when used concurrently.

With this evidence, it is possible now to purpose that administration of Glibenclamide in pretreated Ofloxacin may alter the hypoglycemic effect of Glibenclamide. By this, we may accomplish that when Glibenclamide administered along with Ofloxacin, the hypoglycemic effect is enhanced with respect to time. The blood glucose level should be monitored closely and the dose of Glibenclamide needed to be adjusted during initiation and discontinuation of Ofloxacin therapy.

A limitation of our study was that we did not explore the pharmacokinetic interaction of both drugs. So, further research in pharmacokinetic level is expected to contribute in-depth knowledge on both drugs.

CONCLUSION

Polypharmacy is essential for treating a single disease or multiple diseases in a single patient. There is possibility of interaction between those drugs as they are chemical moieties that interact not only with their specific receptors but may also with other biochemical. This leads

to occurrence of other drug-drug interactions. According to reports, the incidence of interaction ranges up to 20% in patients receiving more than 10 drugs. It is the fourth to sixth leading cause for death in United States.

Hence, the present study is planned with the objective to study the influence of Ofloxacin on hypoglycemic of Glibenclamide in normal wistar rats.

The whole study was divided in to 2 phases.

In the first phase, the influence of Glibenclamide (0.45mg/kg) on the fasting blood glucose levels in normal rats were established and the influence of treatment of Ofloxacin (3.33 mg/kg) on the hypoglycemic activity of Glibenclamide (3.33mg/kg) were studied. In second phase, the influence of Ofloxacin alone on fasting blood glucose levels in normal rats was assessed. Finally, rats were used to find out the drug-drug interactions of Ofloxacin (3.33 mg/kg) and Glibenclamide (0.45 mg/kg) by administering Glibenclamide to the Ofloxacin pretreated rats.

Similarly, multiple dose interaction study was performed in which Ofloxacin (3.33mg/kg) administered concurrently for a week and then the influence on hypoglycemic activity of Glibenclamide (0.45 mg/kg) was assessed on 8th day. Ofloxacin treatment potentiated the hypoglycemia induced by Glibenclamide.

This suggests that it is essential to monitor blood glucose levels in diabetic when Ofloxacin is prescribed in those who are taking Glibenclamide.

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