Section: Pharmacology

Original Research Article

NORFLOXACIN EFFECT ON BLOOD GLUCOSE LEVELS IN EUGLYCEMIC ALBINO RATS

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Abstract

Background: Fluoroquinolones are commonly used in treatment of hospital acquired infection. Many studies have discovered that fluroquinolones were associated with higher risk of both hypoglycemia and hyperglycemia. Norfloxacin is commonly used alone or in combination without their antibacterial drugs in the empiric treatment of many infections, but there is no consensus on its effects on glycemic levels. **Materials and Methods:** Twelve Swiss albino rats of either sex weighing between 150 – 200 g were selected from central animal facility. Animals were randomly divided into 2 groups with six in each group. The control was given Distilled water (25ml/kg body weight orally) and test group was given norfloxacin (50mg/kg bodyweight orally) for 5 days. On fifth day after following overnight fasting, 1 hour after the last dose of the respective drug, oral glucose tolerance test (OGTT) was performed. Glucose (0.6gm/kg body weight) was dissolved in water and was administered to all the rats orally. At 0 minute, 60 minute and 150 minute, the rat tail clipping method was used to measure capillary blood glucose using a standardized glucometer. **Result:** Norfloxacin group showed lower CBG levels at all time intervals of OGTT as compared to the Control group i.e., 0, 60 and 150 minutes. **Conclusion:** Norfloxacin when given orally for 5 days showed fall in blood glucose level in swiss albino rats.

INTRODUCTION

Diabetes is a chronic metabolic disease whose frequency has increased and has become the greatest public health challenge of the 21st century. India has the second highest number of diabetics. According to 2023 data from the Indian Council of Medical Research on Diabetes (ICMR INDIAB), the prevalence of diabetes is 101 million.[1]

Fluoroquinolones are antimicrobial agents that inhibit bacterial DNA synthesis and are used to treat various bacterial infections. Fluroquinolones are broad-spectrum antibiotics and are often prescribed to treat community-acquired pneumonia and urinary tract infections. Increased use of these drugs has resulted in rare and serious side effects such as QT prolongation, tendon rupture, and dysglycemia.[2,3] Studies have shown that these classes of antibiotics may increase the risk of severe hypoglycemia in users of glipizide or glyburide. Several studies have reported an association between fluoroquinolone use and severe dysglycemia (hypoglycemia or hyperglycemia) that can lead to irreversible brain damage or even death.[4] Although hypoglycemia has been reported with most fluoroquinolones. It has been observed that hypoglycemia was related to elevated blood levels of fluoroquinolones and that advanced or impaired renal function, which can also cause high blood levels of fluoroquinolones, are risk factors for the development of hypoglycemia.[5,6] Fluoroquinolone-induced hypoglycemia is not a common side effect. However, it has been reported with most available medications and appears to be more common in elderly patients with a history of type 2 diabetes receiving oral sulfonylureas. Several case reports have described fatal hypoglycemia associated with the use of levofloxacin and norfloxacin.[7,8]

Hypothesis: The exact mechanism of this effect is unknown but is postulated to be a result of blockage of Adenosine 5'-Triphosphate (ATP)-sensitive potassium channels in pancreatic β-cell membranes.[7] Many studies have postulated that pancreatic β-cells causes insulin secretion in concentration dependent manner. Insulin secretion from β-cells is associated with rise of cytosolic Ca2+ concentration ([Ca2+]c). An elevation in [Ca2+] c was observed when fluoroquinolones was given, via

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inhibition of KATP channels and activation of L-type voltage-dependent Ca2+ channels (VDCC). On the other hand, intracellular Ca2+ stores have also been contributed to physiological insulin secretion.[9]
Hence the current study has been taken to evaluate flouroquinolones for their effect on blood glucose levels in euglycemic rats.

MATERIALS AND METHODS

The study was conducted after the approval of IAEC (Institution Animal Ethical Committee). The committee approval number: JSSMC/IAEC/14/5655/DEC2014.
Albino rats of both sexes with an average weight of 150-200 g, aged 4-5 months, were randomly selected from the animal center of JSS Academy of Higher Education, Mysuru and divided into two groups, control and test groups, with 6 rats in each group. Animals were acclimatized for 10 days before being used in the experiment. They were kept in a room with a 12-hour light/dark cycle and temperature control. Animals were maintained on a standard dry pellet diet and water ad libitum. The study was conducted at the Department of Pharmacology during August 2014. For at least an hour before the experiment, the animals were subjected to acclimatization to the environment in the laboratory and then utilized during the experiments. Drug dosage was calculated considering the maximum human dose, which was converted to the animal dose using a formula.[10]
Chemical and drugs: Norfloxacin 50 mg/kg was given after dissolving in distilled water and immediately administered orally, distilled water was administered orally, 0.6 mg/kg glucose was mixed with distilled water for OGTT. Twelve wistar albino rats were randomly divided into 2 groups, with 6 animals in each group (n = 6) [control and experimental group]. The test drug norfloxacin 50 mg/kg/day and distilled water 25 ml/kg/day were administered orally.
Group1: -Distilled water- 25ml/kg/day (orally)
Group2: -Norfloxacin50mg/kg/day (orally)
On the fifth day OGTT was performed. All rats were fasted overnight and one hour following the last dose of each medication, the rats received glucose (0.6 g/kg body weight) orally by gavage. Capillary blood glucose (obtained via tail cut or snip) was measured and assessed at different time intervals (0 min, 60 Min and 150 min) by using a glucometer
OGTT is a test to assess, effects on insulin secretion and glucose regulation in normal rats. In 1925, Du Vigneaud and Karr described the study regarding, carbohydrate utilization and disappearance from the blood. With some modifications of this method we performed OGTT.[11]
Statistical Analysis: Within the same group the Mean value, Standard Deviation (SD) and analysis of variance (ANOVA) were calculated at 0 min 60 min and 150 min. Inbetween the two groups sample t test was run. The values of the test were compared at 0.05 level of significance and for the corresponding degrees of freedom. P<0.05 will be considered as significant. All the statistical analysis was done by using IBM SPSS 21 software.

RESULTS

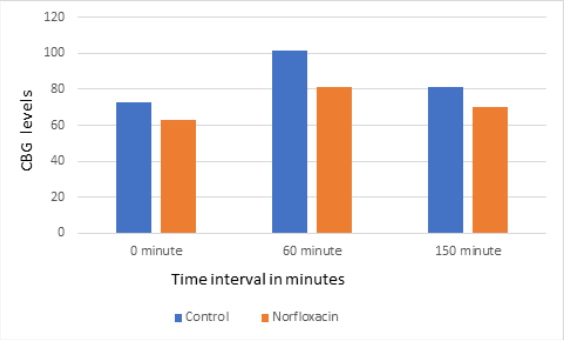

Figure 1: Depicts Capillary Blood Glucose (CBG) levels of control and test groups at different time intervals. Bar diagram showing the effect of norfloxacin on plasma glucose concentration euglycemic rats compared to control at 0, 60 and 150 minutes.

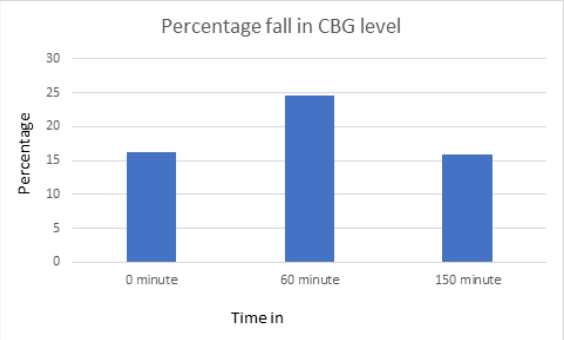

Figure 2: Bar diagram showing percentage fall in the capillary blood glucose levels (CBG) levels in the test group when compared to control group at various time intervals.

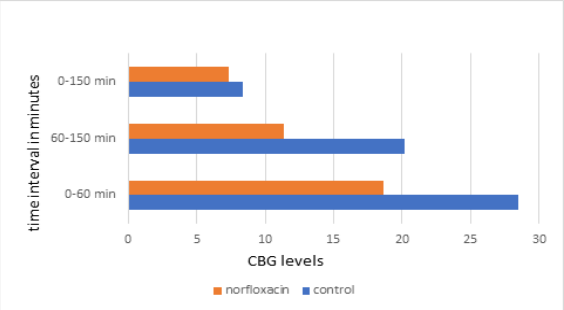

Figure 3: Bar diagram showing CBG levels in the test group and control group at various time intervals.

Compared to control group, a significant decrease in blood glucose levels was observed in Norfloxacin group at all time intervals, maximum fall being at 60 minute (20±0.21) which was statistically significant(p=<0.05) [Table 1 & Figure 1 and 2].
The peak percentage of fall in CBG levels was at 60 minute (24.53%). At 0 minute and 150 minute the percentage of fall in blood glucose concentration were almost similar [Table 2].

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The norfloxacin group showed a reduction in blood glucose concentration throughout the OGTT compared to control group, with a significant decrease in blood glucose observed at 60 minute. [Table 3]

In the norfloxacin, CBG levels remained lower than in the control group but CBG levels changed less from 0 to 150 minute. At 0-60minute and 60-150minute the inter-interval differences was more when compared to the control group was statistically significant [Table 1 and Figure 3].

Table 1: Capillary Blood glucose (CBG) levels in control, and Norfloxacin group and the difference between the control and Norfloxacin group at corresponding time intervals.

Time interval during OGTT	Capillary Blood glucose concentration in mg/dl		
	Control group N=6	Norfloxacin group N=6	Fall in CBG levels Norfloxacin Group compared to control group
0min	73±3.57	62.83±2.31	10.16±1.26
60min	101.5±2.66	81.5±2.88	20±0.21*
150min	81.33±2.16	70.16±2.78	11.16±0.62*

Values are Mean± SD(n=6). *P<0.005

Table 2: Percentage fall in Capillary Blood glucose (CBG) level in Norfloxacin group when compared to control.

Sl no	0min	60min	150min
Norfloxacin	16.18	24.53	15.91

Values are in percentage

Table 3: The difference in the CBG levels of norfloxacin and control group at time intervals 0 min,60 minand150 min of OGTT.

Sl no	OGTT time interval of control-OGTT time Interval of Norfloxacin(C-T)	Difference in CBG values (mg/dl)
1	0-0min	10.16667
2	0-60min	8.5
3	0-150min	2.83
4	60-0min	38.66
5	60-60min	20
6	60-150min	31.33
7	150-0min	18.5
8	150-60min	0.16
9	150-150min	11.16

Values are in mg/dl

Table 4: The difference in the CBG levels within norfloxacin and control group at time intervals 0min,60 minand150 min of OGTT.

Sl no	Time interval	Change in CBG values	
		Control	Norfloxacin
1	0-60min	28.5±0.91	18.66±0.56
2	60-150min	20.16±0.50	11.33±0.09
3	0-150min	8.33±1.41	7.33±0.47

Values are Mean± SD(n=6).

DISCUSSION

In 2006, gatifloxacin was withdrawn from the market due to safety and efficacy concerns. The incidence of hypoglycemia induced by quinolones in the literature varies by class, but compared to other quinolones, gatifloxacin was associated with greater effects of insulin elevation and blood glucose lowering.[12] Therefore, we conducted a study to determine the blood effects of; norfloxacin. glucose levels in normolycemic albino rats.

Early phase insulin response to glucose is impaired in Impaired Glucose Tolerence (IGT) patients. In isolated IGT, basal insulin secretion is normal, but glucose-stimulated first and second phase insulin secretion and (peripheral) insulin sensitivity is reduced. Loss of early-phase insulin release during and after the meal phase has several detrimental effects on normal glucose homeostasis: hepatic glycogenolysis and gluconeogenesis are insufficiently inhibited and muscle glucose uptake is insufficient. This results in postprandial hyperglycemia, which is seen in patients with glucose intolerance and type 2 diabetes. The first phase insulin secretion and basal insulin secretion are impaired in isolated IFG, whereas the second phasing insulinogenesis and peripheral (mostly muscle) sensitivity are normal.[13]

In pancreatic β-cells, glucose stimulates insulin secretion by activating and amplifying signals. This involves a sequence of events such as glucose synthesis by oxidative glycolysis, an increase in the ATP- ADP ratio, K+- sensitive AMP (KATP) channel closure, membrane depolarization and voltage opening. Ca2+ activation of channels, Ca2+ entry, increase in cytoplasmic free Ca2-I and activating exocytosis machinery. Concentration based insulin secretion is maintained by glucose,

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under these conditions. The heightened secretion is highly sensitive to glucose, with the glucose concentration of only 1-6 mmol/L, necessitating glucose transfer and not involving long-chain acyl-CoAs. The potential is to increase the concentration of Ca2+ in the exocytosis of insulin granule. There is a distinct hierarchy between the two approaches. The trigger pathway dominates the gain pathway, and remains silent unless it raises [Ca2+]i in the primary pathway. That is, until the glucose reaches a threshold concentration. Potentiation enhances the secretory response to both glucose and non glucose (amino acid) stimuli. In type 2 diabetes β-cells are damaged. The restoration of insulin secretion in type2 diabetes may be aided by new drugs that correct defective activating pathways, as well as those that enhance signaling via K+ATP channels.[14] K+ATP channels in pancreatic beta cells are critical regulators of insulin secretion. Blocking these channels causes a series of events that trigger the release of insulin. KATP channel has two subunits SUR 1 and kir6.2. Gatifloxacin, temafloxacin and levofloxacin directly inhibit the kir6.2 subunit. In animal models, gatifloxacin and temafloxacin have been shown to block KATP channels more potently than levofloxacin, resulting in significant stimulation of insulin secretion.[15]

In the present study [Table 1 and Table 2], norfloxacin group demonstrated a decrease in capillary blood glucose levels at different time intervals than the control group during OGTT, which were 0 minute, 60 minute and 150 minute. Compared to control, capillary blood glucose concentration difference at 0 min is 10.16±1.26 i.e., 16.18%, which indicates indirectly, that norfloxacin increased basal secretion of insulin. The reduction in the capillary blood glucose level at 60 min is 20.83±0.21 when compared to control i.e., 24.53%which indicates that norfloxacin causes more glucose dependent insulin secretion from pancreatic β cells. The difference in the CBG level at 150 min is 11.16±0.62 when compared to control i.e., 15.91 % because of sustained action of norfloxacin on pancreatic β cells. The quantum of fall in blood glucose concentration of norfloxacin group at 0 min and150 min is almost equal.

In [Table 3], The inter interval difference of norfloxacin group at 0-60 min is maximum, which indicates glucose dependent insulin release and inter-interval difference at 60-150 min of norfloxacin group is more compared to 0-150 min because of sustained effect on pancreatic β cell. The interval difference at 0-150 min is the total combined effect of norfloxacin on pancreatic β cells.

The above findings indicate that norfloxacin acts as a hypoglycemic drug in normal albino rats. OGTT test is used to assess insulin sensitivity and glucose tolerance, which indicates beta cell function.

CONCLUSION

Norfloxacin showed a reduction in capillary blood glucose levels in euglycemic albino rats by OGTT compared to controls. The hypoglycemic activity of norfloxacin was greatest after 60 minutes, justifying the above-mentioned mechanism and improving glucose-dependent release of insulin. Thus, it can be concluded that norfloxacin induces insulin secretion from pancreatic β-cells in a concentration-dependent manner. Glucose-induced insulin secretion from β-cells is closely related to an increase in cytosolic Ca2+ concentration ([Ca2+]c) and causes a decrease in blood glucose concentration.

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