Evaluation of Glucose Homeostasis Abnormality Associated with use of Moxifloxacin in Rats

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ABSTRACT

Objectives: Present study is undertaken to investigate the effect of Moxifloxacin on serum glucose concentration in normal and diabetic rats in order to confirm Moxifloxacin induced homeostasis abnormalities and to identify probable mechanism responsible. Materials and Methods: Wistar rats weighing 150-220g used in the present study. These animals were randomly divided into 4 groups as Normal control, normal rats treated with Moxifloxacin, in remaining rats diabetes was induced by the administration of alloxan. Those rats showing blood glucose level more than 160mg/dl were included in the study and divided into diabetic control and diabetic rats with moxifloxacin. Blood samples were collected from these rats and subjected to blood glucose and serum insulin levels estimation. Results: Blood glucose were reduced and increased insulin levels significantly after 1st and 2nd hours of moxifloxacin administration. Conclusion: Moxifloxacin treatment results in hypoglycaemia all both diabetic and non-diabetic rats. So, physicians should consider this riskand prescribe moxifloxacin cautiously.

Keywords: Moxifloxacin; Alloxan induced diabetes; Hypoglycaemia; Blood glucose

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INTRODUCTION

Quinolones are the most commonly used antimicrobials for urinary and respiratory tract infections. Most commonly used fluoroquinolones include ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin. Fluoroquinolones are usually safe drugs and produce mild gastrointestinal and CNS disturbances. Therefore, discontinuation of quinolones therapy during clinical trials is uncommon. However, several recent events have raised questions about their safety [1]. Several fluoroquinolones have been withdrawn from US market because of adverse effects produced by them. These include temofloxacin which produced haemolysis, renal failure and hypoglycaemia [2]. Trovofloxacin which produced hepatotoxicity and liver failure [3]. Grefafloxacin produced cardiac arrhythmias "torsade de pointes" due to Q-T interval prolongation [4], whereas sparfloxacin produces phototoxicity and torsade de pointes [5]. Levofloxacin because of its phototoxicity and CNS adverse effects is used to the limited extent [6]. Each of this quinolone has demonstrated safety in pre-approved clinical trials that have enrolled several thousand patients. Serious but uncommon adverse effects were detected only after drug were administered to large patient populations [1]. Moxifloxacin is fourth generation fluoroquinolone has a broad-spectrum activity against gram+VE, gram -VE and anaerobic bacteria.It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell replication. Moxifloxacin (Avelox) was approved by US FDA in 1999 [7]. It has been used for treatment of various infectious diseases. Fluoro-quinolones have been widely used for treatment of community and hospital-acquired infections. These drugs are known to cause

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glycaemic disturbances. Gatifloxacin was banned on 18/3/2011 in India because it poses 17 times higher risk of developing serious hyperglycaemia [8]. Although uncommon, hypoglycaemia has also been reported with fluoro-quinolones [9]. Hypoglycaemia typically occurs within the 1st 3 days of fluoro-quinolone therapy and has also been reported after the first dose of either intravenous or oral administration [10,11]. In a case of oxacin induced hypoglycaemia the serum levels of immunoreactive insulin [IRI] were found to be increased during hypoglycaemia episodes. This is most probably due to release of insulin from pancreatic islets by inhibiting ATP sensitive K-channels of pancreatic β-cells [12]. This supports the hypoglycaemia produced by increase in insulin release. Moxifloxacin has been considered to be safe as far as hypoglycemia is concerned. Only two case has been reported for moxifloxacin-induced hypoglycemia one is non-diabetic patient [13] and Case of hypoglycemia associated with moxifloxacin administration in a patient with diabetes, pneumonia and multi-organ failure also reported [14]. Therefore, this study is under taken to investigate effect of moxifloxacin on glucose homeostasis in normal and diabetic rats in order to clarify the mechanism of moxifloxacin induced abnormalities in glucose homeostasis.

MATERIALS AND METHODS

The study was carried out in a male Wister rats weighting150-220gm and was performed in accordance with guidelines of normal experimentation [as per as CPCSEA guidelines]. Study was reviewed and approved by Institutional Animal Ethics Committee (IAEC). All the animals wererandomly divided into four groups of 8 rats each (n=8).
Group 1: Non-diabetic rats[control] will receive equivalent volume of normal saline**.**
Group 2: Non-diabetic rats [Test] Will receive 50mg/kg moxifloxacin I.P.
Diabetes was induced in two groups of 8 rats each by I.P. injection of Alloxan in the dose of 120mg/kg into overnight fasted rat. 48hr later rats with an overnight fasting serum glucose levels above 160mg/dl were taken for the study.
Group 3: Diabetic rats [control] will receive equivalent volume of normal saline.
Group 4: Diabetic rats [Test] will receive 50mg/kg moxifloxacin I.P.
Blood samples were collected from all the groups at 0,1hr, 2hr, 4th hr & 6^{th}hr for the estimation of serum glucose and serum insulin levels.

STATISTICAL ANALYSIS

All the data will be expressed in ± SEM. Difference in the mean groups will be evaluated by using Analysis of variance (ANOVA). Statistical significance will be set at $p<0.05$.

RESULTS

Blood glucose levels in both normal and diabetic groups were decreased from the 1hr after the moxifloxacin administration but this decrease was statistically significant only in diabetic rats at 2hr and was returned to normal from 3hr (Figure 1).
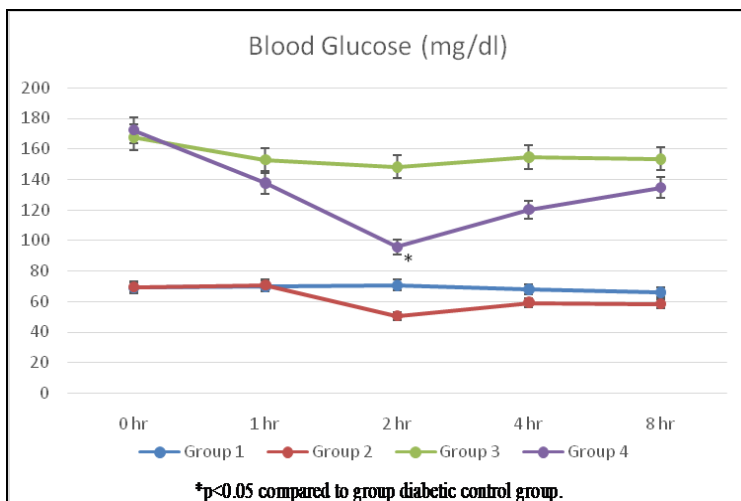

Figure 1: Shows blood glucose levels in all groups

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Figure 2 shows significant decrease of serum insulin levels in diabetic groups from the 0hr and slight increase in serum insulin levels after 2hr of moxifloxacin administration. However, this increase was not achieved statistical significance.
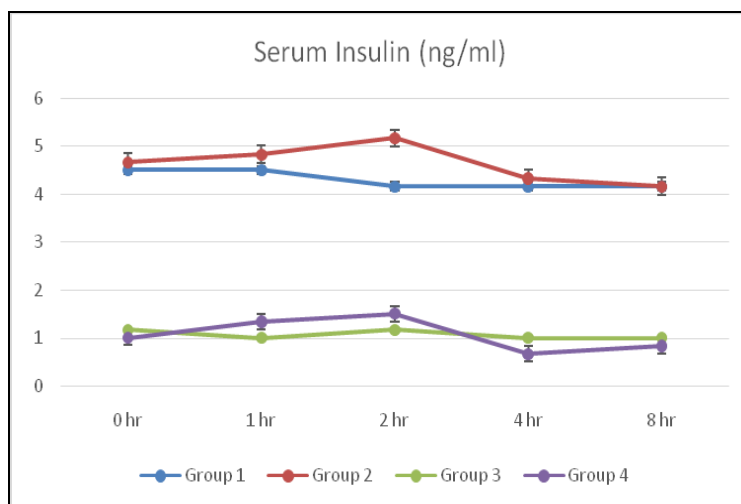

Figure 2: Shows serum insulin levels in all groups

DISCUSSION

High glucose levels trigger a series of reactions that ultimately lead to insulin secretion by islet β-cells. The transformation and utilization of glucose increase the intracellular ratio of ATP/ADP causing K_{ATP} channels to close. This leads to depolarization of cell membrane causing voltage-dependent calcium channels to open, which further leads to an increase in the concentration of free intracellular calcium. Then, insulin is released. In addition to K_{ATP} channels [15], other voltage gated potassium channels are expressed in pancreatic β-cells and regulate insulin secretion by repolarizing membranes [16]. Among the fluoroquinolones, ciprofloxacin, gatifloxacin and levofloxacin are found to be associated with severe disturbances with glucose metabolism [17]. As of now, adverse events of dysglycemia were associated with moxifloxacin but causal relationship had not been established in most of these events [17,18]. Animal and *in vitro* studies have shown that fluoroquinolones increase insulin release by blockingadenosine triphosphate (ATP) sensitive potassium channels and cause depolarization of pancreatic β cells. It leads to the opening of the voltage gated calcium channels and causes calcium movement through β cells and release of insulin [19,20]. In our study, moxifloxacin probably act through above mechanism to cause hypoglycemia and increasedinsulin levels within hours of drug consumption which is consistent with hyper insulinemic hypoglycemia in previous studies [21]. Temporal association, the reappearance of event on subsequent administration and no other confounding factor that can contribute to cause hypoglycemia make this reaction more likely due to moxifloxacin.

CONCLUSIONS

In conclusion, our results showed decreased blood glucose levels and increased serum insulin levels in both diabetic and non-diabetic rats within few hours of moxifloxacin administration. Clinicians should consider this risk when treating patients with diabetes and prescribe moxifloxacin cautiously.

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