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EVALUATION OF LEVOFLOXACIN VS. NORFLOXACIN; EFFECT ON BLOOD GLUCOSE PROFILE IN ALLOXAN INDUCED DIABETIC ALBINO RATS- A COMPARATIVE STUDY

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ABSTRACT: Flouroquinolones (FQ) used commonly for treatment of community and hospital-acquired infections, has been prefixed with multiple adverse effects. Amongst them the glycemic variability has been attention seeking. Drug induced dysglycemia can be acute or persistent and severe too. The present study is designed to evaluate and compare the actions of Levofloxacin vs. Norfloxacin in altering blood glucose levels in Alloxan induced diabetic albino rats. 30 albino rats with fasting blood sugar (FBS) in the range of 80-115 mg/dl were induced diabetes with intraperitoneal Alloxan (150mg/kg body wt). After 7 days of induction, the rats that developed a stable hyperglycemia with FBS≥250 mg/dl were selected for the study. Following administration of test and standard drug FBS levels were measured on days 0, 3, 7, 14 & 28 using glucometer. Statistically, values in all the groups were analyzed by using one-way analysis of variance (ANOVA), followed by independent T test for group comparisons. P values less than 5% (0.05) was considered as significant. Glycemic variation was found to be statistically significant between glibenclamide + norflox and norflox group alone as similar as in glibenclamide + levofloxacin group and levofloxacin alone group with P<0.001, i.e., HS highly significant.

INTRODUCTION: Fluoro-quinolones have been widely used for treatment of community and hospital-acquired infections. With increase in usage frequency of these drugs, some concerns regarding rare but severe adverse effects, such as tendon rupture, QT interval prolongation and dysglycemia have raised.[1, 2] It has previously been reported that several classes of antibiotics can increase the risk of severe hypoglycemia among users of glipizide or glyburide, as a result of known combined drug effects.[3]

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Therefore, prescribing safe antimicrobial agents with regard to their effects on glucose homeostasis is important due to the risk of dysglycemia episodes associated with infection or sepsis.

A nationwide diabetes cohort study has discovered that fluoroquinolones were associated with higher risk of both hyperglycemia and hypoglycemia, compared to macrolides and cephalosporins in diabetics.Patients who suffered from comorbid chronic kidney disease as well as those who were concomitantly treated with insulin or sulfonylurea were more vulnerable to FQ induced abnormal fluctuations in glucose homeostasis.[4]

Dysglycemia can be persistent and severe but often responds only to discontinuation of quinolones. Gatifloxacin was banned on 18/3/2011 in India

because it poses 17 times higher risk of developing serious hypoglycemia.[5]

Hypoglycemia 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.[6, 7, 8]

Exact mechanism of fluoro- quinolones causing alterations in blood glucose levels is unknown. It has been postulated that glucose alterations may be due to blockage of the adenosine 5'-triphosphate (ATP)-sensitive potassium channels in pancreatic β-cells. This leads to depolarization of the β-cell membrane and opening of voltage-dependent calcium channels allowing calcium movement into the cells with subsequent insulin release. Also insulinotropic effect of fluoroquinolones resulted from the enhanced stimulatory effects of β-cell nutrients, rather than the initiation of insulin secretion.[9, 10]

On the other hand, the mechanism of hyperglycemia is unclear. It may be due to a direct drug effect on glucose metabolism, or it may be a result of multiple confounding factors. In addition, some recent findings imply that disturbed cellular glucose transport and GLUT1 function may underlie the dysglycemic effects of ciprofloxacin and levofloxacin.[11]

Some animal data present a decrease in secretory granules in pancreatic β cells on exposure to gatifloxacin, which may in turn lead to a decrease in serum insulin levels and resulting in hyperglycemia.[4] In some published cases, serum insulin levels during the episode of hypoglycemia revealed unsuppressed values, suggesting hyperinsulinemic hypoglycemia as the underlying psychopathological mechanism. [12- 15]

Although uncommon, levofloxacin-induced hypoglycemia can be dangerous. Delay in recognizing the etiology of the hypoglycemia lead to rare and serious consequences likepontine-myelonosis, quadriplegia and permanent anoxic brain injury.[16, 17]

Several case reports have indicated that levofloxacin is associated with a slightly higher risk of hypoglycemia than other classes of antibiotics but no study has demonstrated the norfloxacin comparison with levofloxacin in terms of their effect on blood glucose levels.

It remains unclear that which FQ has more effect on blood glucose levels. Therefore an animal model is chosen to demonstrate and compare the effect of different FQ on blood glucose levels because it is ethically more acceptable to study about dysglycemia in animals.

MATERIALS AND METHODS:

Swiss Albino rats of either sex, inbred in the Central Animal House, Department of Pharmacology, J.J.M Medical College, Davangere, under suitable conditions of housing, temperature, ventilation and nutrition were used in this study.

Ethical consideration:

Study protocol was approved by Animal Ethical Committee, Department of Pharmacology, JJM Medical College, Davangere. Animals were handled in accordance with the CPSCEA guidelines.

Methodology:

42 albino rats weighing 170-220g, aged 3-4 months, non pregnant healthy animals with FBS in the range of 80-115 mg/dl, were included in the study. Hyperglycemia was induced using Alloxan monohydrate and blood sugar values were measured with Glucometer. Animals were randomly housed in cages with a 12 hour light: dark cycle with free access to standard pellet and water.

Induction of hyperglycemia:

Following an overnight fasting, 24 rats were injected intraperitonially with the freshly prepared Alloxan monohydrate (5% solution, dissolved in normal saline) at a dose of 150 mg/kg body weight. Alloxan, a urea derivative causes hyperglycemia by selective destruction of β cells of pancreas. Animals with FBS more than 250mg/dl after 1 week of induction were selected and were divided into 4 groups i.e. Glibenclamide, Glibenclamide and Levofloxacin, Glibenclamide and Norfloxacin, Diabetic control with 6 animals in each group.

Drugs and chemicals:

Group 1: Control (normal saline 0.5 ml orally)

Group 2: Levofloxacin control group(100mg/ kg)

Group 3: Norfloxacincontrol group(50 mg/ kg)

Group 4: Glibenclamide(0.5mg/kg orally).

Group 5: Glibenclamide and Levofloxacin (0.5mg/kg+ 100mg/ kg)

Group 6: Glibenclamide and Norfloxacin (0.5mg/kg +50 mg/ kg)

Group 7: Diabetic control (Alloxan monohydrate 5% i. p, 150mg/kg)

Group 1 received normal saline on the day of induction and then after a gap of one week for further 28 days.

Group 4, 5, 6, 7 received Alloxan monohydrate on the day of induction.

After 1 week of induction,

Group 4, 5, 6 received Glibenclamide (0.5mg/kg orally) for 28 days.

Group 2, 5 received Levofloxacin100mg/ kg for 28 days.

Group 3, 6 received Norfloxacin50 mg/ kg for 28 days.

Estimation:

FBS levels were recorded on 0 day, 3rd, 7th, 14th and 28th day by using Glucometer. Blood was drawn from the rat tail vein and FBS values were represented in mg/dl units.

Statistical analysis:

The data obtained from the study were subjected to statistical analysis, from which mean, standard deviations were calculated for each group. One way ANOVA was used for multiple group comparisons and independent T test comparing 2 groups. P values less than 5% (0.05) was considered as significant.

RESULT:

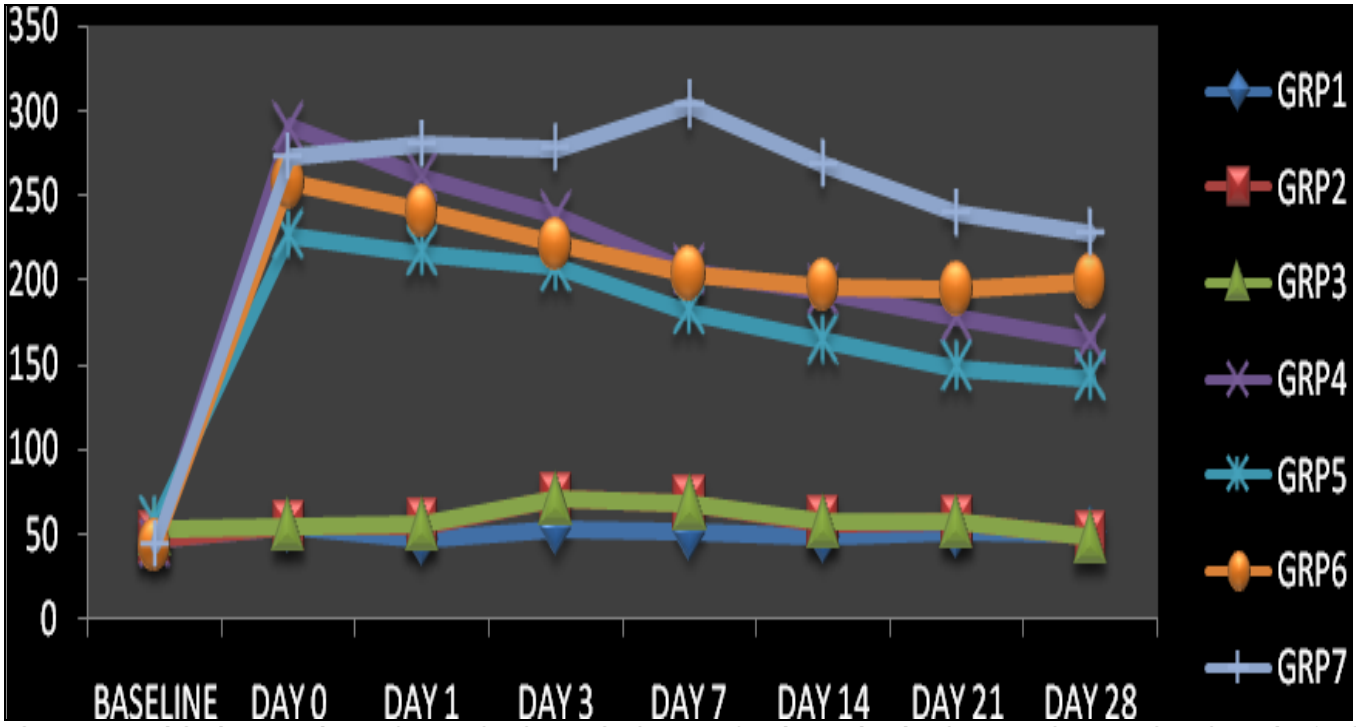

FIG.1: LINE DIAGRAM 1: DIABETIC INDUCTION IN GROUP 4,5, 6, 7 AND VARIATION IN FBS LEVELS FROM DAY 0 TO DAY 28 IN ALL THE GROUPS FOLLOWING TEST AND STANDARD DRUG ADMINISTRATION.

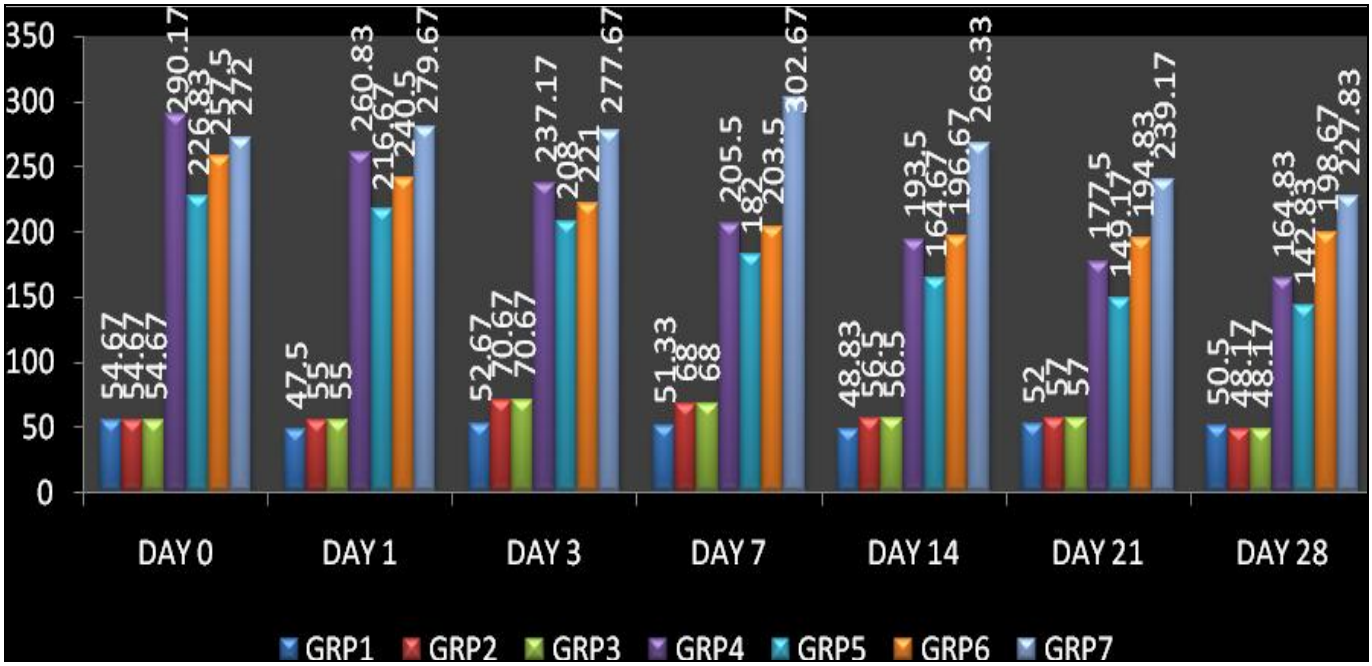

FIG.2: BAR DIAGRAM 1: SHOWING DAY- WISE MEAN VARIATION IN BLOOD GLUCOSE LEVELS IN VARIOUS STUDY GROUPS.

TABLE 1: STATISTICAL ANALYSIS SHOWING COMPARISON OF DIFFERENCE IN BLOOD GLUCOSE LEVELS BETWEEN GROUP 2 AND GROUP 5 ON DIFFERENT DAYS

Days	Groups	Mean±SD	Mean Difference	t-Value	Significance
0-3	2	-16±9.011	-34.83	-4.634	P=0.001, HS
	5	18.83±16.055			
0-7	2	-13.33±11.587	-58.167	-8.32	P<0.001, HS
	5	44.83±12.608			
0-14	2	-1.83±12.828	-64	-5.915	P<0.001, HS
	5	62.17±23.190			

TABLE 2: STATISTICAL ANALYSIS SHOWING COMPARISON OF DIFFERENCE IN MEAN BLOOD GLUCOSE LEVELS BETWEEN GROUP 3 AND GROUP 6 ON DIFFERENT DAYS

Days	Groups	Mean±SD	Mean Difference	t-Value	Significance
0-3	3	-16.00±9.011	-52.50	-7.319	P<0.001, HS
	6	36.50±15.083			
0-7	3	-13.33±54.00	-67.33	-8.476	P<0.001, HS
	6	54.00±15.633			
0-14	3	-1.83±12.828	-62.67	-7.494	P<0.001, HS
	6	60.83±15.968			

TABLE 3: STATISTICAL ANALYSIS SHOWING COMPARISON OF BLOOD GLUCOSE LEVELS BETWEEN GROUP 5 AND GROUP 6 ON DIFFERENT DAYS

Days	Groups	Mean±SD	Mean Difference	t-Value	Significance
0-3	5	18.83±16.655	-17.667	-1.964	P=0.078, NS
	6	36.50±15.083			
0-7	5	44.83±12.608	-9.167	-1.118	P=0.290, NS
	6	54.00±15.633			
0-14	5	62.17±23.190	1.333	0.116	P=0.910, NS
	6	60.83±15.968			

TABLE 4: DAY WISE VARIATION IN MEAN SUGAR VALUES

	Day 3- Day 0	Day7- Day 0	Day14- Day 0
Group 2	16	14	2
Group 3	16.5	13	2.3
Group 4	43	84.67	94.67
Group 5	2	24.83	42.16
Group 6	36.5	54.5	60.83
Group 7	5.6	30.67	9.67

RESULTS:

Line diagram 1 reveals that diabetic groups show more glycemic variations than non-diabetic groups 1, 2, 3. FQ administration in diabetic rats showing more mean glycemic variability on day 3 and 7 mean in comparison to other days.

Table 1 shows difference in mean glycemic variability which is statistically highly significant on day 3, 7, 14 between group 2 and group 5 which signifies that levofloxacin (FQ) induces more blood sugar variation in diabetic rats (on glibenclamide). **Table 2** also shows difference in mean glycemic variability which is statistically highly significant on day 3, 7, 14 between group 2 and group 5 which signifies that norfloxacin (FQ) induces more blood sugar variations in diabetic rats (on glibenclamide). **Table 3** highlights that the glycemic variability between norfloxacin and levofloxacin combination groupswasn't statistically significant.

Results in **Table 4** reveal the hypoglycemic action of glibenclamide, progressively increasing from day 3 to day 14 and acting as a better drug for glycemic control. On day 7 and day 14 levofloxacin combination group shows more glycemic variability than levofloxacin alone group. Norfloxacin combination group also shows much glycemic variability on day 3, 7, 14 in comparison to Norfloxacin alone group. Group 7 induced with alloxan alone exhibits that hyperglycemic actions reaching peak around day 7 subsequently starts waning due to beta cell regeneration.

DISCUSSION: The glycemic control issue with fluoroquinolones became a concern in 2006 when Bristol-Myers Squibb stopped manufacturing Tequin® (gatifloxacin).[18] Although most of the effects on glucose homeostasis have been linked to gatifloxacin, it should be noted that all fluoroquinolones can cause blood glucose fluctuations [19, 20, 21]. Hence we performed a comparative study of glycemic variability using levofloxacin and norfloxacinin both diabetic and non-diabetic alibino rats. The glycemic variation was found to be statistically significant among norfloxacin with glibenclamide group and norfloxacin group alone. Also comparison of group 3, 6 i.e. levofloxacin with glibenclamide group and levofloxacin alone revealed statistically significant glycemic variability with $P<0.001$, i.e., HS highly significant.

But there was no statistically significant difference between glibenclamide with norfloxacin group and levofloxacin with glibenclamide group indicating that both FQ are almost equally prone for glycemic variability.

Our results identify that glycemic variblity is more during early days after FQ administration i.e. day 3 to 7, occurring at almost similar rates in both FQ s but more in diabetic rats (on glibenclamide) than non-diabetic rats.

CONCLUSION: Our results reveal that both levofloxacin and norfloxacin are more prone for glycemic variability especiallyin diabetic rats with antidiabetic medications. Subjecting results to human beings, clinicians should remain vigilant when prescribing FQ, especially, but not only for patients who are prone to dysglycemic events. Early recognition of FQ as the possible cause of dysglycemia could prevent many patient from potentially suffering life-threatening consequences.

Previously no studies have reflected about norfloxacin's action on blood glucose levels and also many studies in past concluded that levofloxacin carried higher risk compared to other fluoroquinolones, but with our present study we could derive that both levofloxacin and norfloxacin might carry a similar risk of glycemic variability. On power with other studies we could also derive at a conclusion that diabetic individuals are more prone for glycemic variability than non-diabetic individuals following FQ administration.

More frequent monitoring of blood glucose levels, especially early in the course of FQ therapy, seems advisable in order to prevent unfortunate events. Thus monitoring of blood glucose is recommended when these agents are co-administered especially in diabetic individuals. Preferably in situations where blood glucose monitoring isn't feasible non FQ antibiotics should be preferred.

To conclude, dysglycemia is adangerous adverse event associated with the fluoro-quinolones. It appears to be more common in elderly patients with

a history of type 2 diabetes who are receiving treatment with an oral sulfonylurea. It can be persistent and severe and often responds only to discontinuation of quinolones. Therefore, clinicians should recognize this potential adverse effect and should monitor blood glucose more frequently, especially early in the course of therapy.

Limitations: hypoglycemia and hyperglycemia has not been assessed separately.

CONFLICT OF INTEREST: None

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