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A STUDY TO EVALUATE THE EFFECT OF GATIFLOXACIN ON BLOOD SUGAR LEVELS IN DIABETIC AND NON DIABETIC RABBITS – A CHRONIC PROSPECTIVE STUDY

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ABSTRACT

Introduction: The aim of the study is to evaluate the effects of gatifloxacin alone and in combination with glyburide on blood sugar levels in non-diabetic and alloxan induced rabbits. **Methods:** 24 hrs fasting animal's blood was collected for baseline investigations. After blood collection, alloxan was induced intravenously in 32 out of 40 rabbits. On day 2 FBS was repeated and other investigations were repeated on day 3. FBS and S. Insulin were repeated on day 7 of treatment. On day 14 of treatment (end day of treatment) the above mentioned investigations were repeated again. **Results:** After alloxan induction, FBS levels of gr-I, gr-II, gr-III, gr-IV at baseline were 93.63, 94.13, 93.88, 93.13 mg/dl, 24 hours after alloxan induction were 220.63, 220.86, 220.87, 220.88 mg/dl, 48 hours after alloxan induction were 221.13, 221, 222, 221 mg/dl. S.Insulin levels for the groups for baseline were 3.84, 3.78, 3.74, 3.79 mg/dl; 48 hours after alloxan were 1.80, 1.81, 1.80, 1.83 mg/dl. FBS levels after 2 weeks of Gatifloxacin medication in gr-III and gr V for baseline were 222, 93.63 mg/dl, at 1week were 220.75, 93.25mg/dl, at 2 weeks were 220.38, 93.38 mg/dl. S. Insulin levels for both above groups and after 2 weeks of gatifloxacin medication for baseline were 1.80, 3.76 mg/dl, at 1 week 1.82, 3.77mg/dl, at 2 weeks 1.84, 3.78 mg/dl. **Conclusion:** Gatifloxacin, at therapeutic doses, had no effect on blood glucose levels or insulin levels, even on prolonged intake, both in diabetics and non-diabetics. Concurrent administration of gatifloxacin and glyburide did not significantly reduce blood glucose concentrations, than when glyburide is administered alone, in diabetics. Gatifloxacin should be avoided as an outpatient or as an over the counter drug. It may, be used on an inpatient basis as the recipient is under medical observation.

KEYWORDS: Diabetes Mellitus, Alloxan, Gatifloxacin, Glyburide, FBS, Insulin.

INTRODUCTION

Diabetes mellitus is a condition characterized by chronic hyperglycemia and disturbance of carbohydrate, fat and protein metabolism associated with absolute or relative deficiencies in insulin secretion and /or action.[1] The two broad categories of DM are designated as type 1 and type 2.[2] Type I diabetes is treated with insulin[1,2], while type II is treated by dietary modification, exercise, oral hypoglycemic drugs (sulphonylureas, biguanides, glitazones etc.) and one third may ultimately require insulin.[3] Glyburide (sulfonylurea) is one of the commonest oral hypoglycemic agents to be prescribed to Type II diabetic patients.[4] It is administered at a dose of 1.25 to 20 mg/day. Its duration of action lasts 12 to 24 hours. The commonest complication caused by glyburide and such other oral hypoglycemic agents, is hypoglycemia. Gatifloxacin is given orally and intravenously.[5] Gatifloxacin a fluoroquinolone targets bacterial DNA gyrase and topoisomerase IV. Anti-topoisomerase and anti DNA gyrase activity of fluoroquinolones inhibits the gram positive and gram negative organisms.[6] Several pre and post marketing studies have revealed a probable role of gatifloxacin in causing dysglycemia, i.e. both hypo and hyperglycemia, in elderly patients (reduced renal clearance).[4] Two retrospective studies, conducted to evaluate the dysglycemic effects of gatifloxacin in patients for respiratory tract infections, also showed similar results.[7,8] Gatifloxacin has been reported to cause fluctuations in blood glucose levels, it may interact with oral hypoglycemic drugs and produce dangerous hypoglycemia. So this study was planned to evaluate the effect of oral gatifloxacin, alone and in combination with glyburide (one of the most commonly prescribed OHA), on fasting blood glucose and serum insulin levels over a 14 day period.

MATERIALS AND METHODS

Chemicals and Drugs

Glyburide was administered in a suspension in 2% gum acacia and dose was adjusted to a volume of 2-5 ml as a single daily dose to the rabbits for duration of 14 days. Clinical dose of glyburide is 5 to 20 mg/day[9] and has been modified to 0.5mg/kg/day.[10] Human dose of tablet Gatifloxacin is 400 mg/day[11] extrapolated to 19 mg/kg/day.[12] In 2% gum acacia an oral suspension of the drug was made and the dose was adjusted to a volume of 2-5 ml daily for rabbits. A combination therapy of Glyburide (0.25mg/kg) plus Gatifloxacin (19mg/kg) oral suspension in 2% gum acacia with dose adjusted to a volume of 2-5 ml daily to the rabbits for 14 days.

Animals

40 Healthy male and female New Zealand albino rabbits weighing above 1.5 kg, above the age of 24 weeks were selected for this study. These animals were housed under standard laboratory conditions in a well-ventilated room and fed on standard pellet diet. The animals had free access to diet & water and were placed in clean, neatly labeled cages containing two albino rabbits in each cage. All animals were procured from the animal house of Department of Pharmacology, Grant Government Medical College and Sir J. J. Group of Hospitals, Byculla, Mumbai. The study was conducted after approval from the institutional animal ethics committee.

Experimental Group

After inducing diabetes with Alloxan, 32 rabbits were randomized into 4 groups, each containing 8 rabbits, while the remaining 8 rabbits were allocated to a fifth group. (Table: 1).

Table 1: Experimental Group

Alloxan induced diabetic rabbits	Group I	Control: 2% gum acacia (2ml/kg/day).
	Group II	Gatifloxacin(19mg/kg/day).
	GroupIII	Glyburide (0.5mg/kg/day).
	Group IV	Gatifloxacin(19mg/kg/day) + Glyburide (0.5mg/kg/day).
Non diabetic rabbits	Group V	Gatifloxacin (19mg/kg/day)

Evaluation Parameters

Collection of Blood Sample

All the albino rabbits were fasted for 24 hours, placed in a rabbit holder and subsequently 5 ml of blood was collected through the marginal ear vein after cleaning with xylene. The blood was placed in a neatly labeled fluoride and plain test tube. The blood samples were kept at room temperature for 2 hours for coagulation to be completed. Subsequently, the two sets of tubes were subjected to centrifugation and the supernatant plasma serum was separated.

Biochemical parameters

Fasting blood sugar was estimated within 24 hours of collection in mg/dl by GOD/POD methods.[13] Insulin estimation was done using 125 I RIA kit.[14] Blood Urea Nitrogen (BUN) was measured using Diacetyl Monoxime Method (DAM).[15] Serum Creatinine was measured by "Jaffe's" Reaction.[16] Estimation of serum glutamate oxaloacetate transaminases and pyruvate transaminases (SGOT/ SGPT) was done enzymatically.[17] Weight of the rabbits were measured on laboratory balance at baseline and then at the end of 2 weeks.

Experimental Design

- Day 1
  - Diabetes Induction
    - Animals were fasted for a period of 24 hours after which 5ml of blood was collected from the marginal ear vein and the following baseline investigations were conducted: FBS, Serum Insulin, Serum Creatinine, BUN, SGOT, SGPT & Body Weight
    - After the blood collection, injection alloxan 140mg/kg was given slowly, intravenously in the marginal ear vein to 32 animals, except 8 rabbits.
- Day 2
  - FBS was repeated
- Day 3
  - Randomization & beginning of study treatment
    - FBS, Serum Insulin, Serum Creatinine, BUN, SGOT & SGPT were repeated. Randomization was done and diabetic rabbits were allocated to one of the 4 treatment groups, if they had: hyperglycemia (blood glucose≥ 200 mg/dl) and study medication was started for all 5 study groups.
- Day 10 (Day 7 of treatment)
  - FBS & Serum Insulin was repeated
- Day 17 (Day 14 of treatment)
  - End of treatment period
    - The following baseline investigations were repeated:
    - FBS, Serum Insulin, Serum Creatinine, BUN, SGOT, SGPT & Body Weight.

Statistical Analysis

All quantitative data are presented as mean ± standard deviation (SD). The treatment groups were analyzed for baseline comparability by ANOVA. Comparison of parameters within and between groups for statistical significance at any given time was done by One-Way

ANOVA. Post-hoc Dunnett's test was applied, to check for significant changes from baseline. For individual comparison of data students't'-test (unpaired't'-test for between group comparison & paired't'-test for within group comparison) were applied. For all tests a 'p' value of <0.05 was considered as statistically significant.

RESULTS

BASELINE DATA

Baseline data in the different study groups was estimated. Values in all the groups were comparable with respect to age, body weight, fasting blood sugar (FBS), serum insulin (S.I.), SGPT, SGOT, BUN and serum creatinine. (Table 2).

Table 2: Baseline data

Baseline data (MEAN ± SD)						
	GR-I	**GR-II**	**GR-III**	**GR-IV**	**GR-V**	**P value**
Age (months)	37.75 ± 0.46	37.75 ± 0.47	37.75 ± 0.42	37.75± 0.45	37.63 ± 0.52	**0.98**
Body wt.(Kg)	1.93 ± 0.02	1.93 ± 0.01	1.93 ± 0.05	1.93 ± 0.01	1.92 ± 0.01	**0.19**
FBS(mg/dl)	93.63 ± 2.92	94.13 ± 2.83	93.88 ± 3.83	93.13 ± 2.83	93.63 ± 2.92	**0.24**
S. Insulin (µ IU/ml)	3.84 ± 0.15	3.78 ± 0.18	3.74 ± 0.10	3.79 ± 0.09	3.76 + 0.12	**0.65**
SGPT (IU/L)	55.56 ± 1.45	55.29 ± 1.74	55.59 ± 1.30	55.57 ± 1.29	55.59 ± 1.11	**0.59**
SGOT (IU/L)	56.01 ± 3.56	55.60 ± 3.27	55.87 ± 3.42	55.91 ± 3.15	55.87 ± 3.15	**0.22**
BUN (mg/dl)	22.48 ± 1.19	22.58 ± 1.16	22.43 ± 1.12	22.39 ± 1.08	22.51 ± 1.15	**0.14**
S. Creatinine (mg/dl)	1.23 ± 0.02	1.23 ± 0.01	1.22 ± 0.02	1.24 ± 0.02	1.23 ± 0.01	**0.35**
Repeat Measures ANOVA applied (p<0.05 taken as significant)						

Control vehicle (Group I): oral 2% Gum Acacia
Control medication (Group II): 0.25 mg/kg Glyburide as an oral suspension in 2% Gum Acacia
Study medication (Group III and V): 19 mg/kg Gatifloxacin as an oral suspension in 2% Gum Acacia
Combination medication (Group IV): 0.25 mg/kg Glyburide and 19 mg/kg Gatifloxacin as an oral suspension in 2% Gum Acacia.

DIABETES INDUCTION IN GROUPS I, II, III AND IV

After intravenous injection of 140 mg/kg Alloxan, in groups I, II, III and IV, the FBS levels were checked at 24 and 48 hours, while the S. Insulin levels were done at 48 hours after induction. The results have been shown in Table 3 and Table 4.

Table 3: Fasting blood sugar levels (mg/dl) after alloxan (140 mg/kg)

FBS (mg/dl, MEAN ± SD)					
	GR- I	**GR- II**	**GR - III**	**GR - IV**	**p value**
Baseline	93.63 ± 2.92	94.13 ± 2.83	93.88 ± 3.83	93.13 ± 2.83	**0.24**
24 hrs after alloxan	220.63 ± 3.74	220.86 ± 3.83	220.87 ± 3.82	220.88 ± 3.83	**0.9**
48 hrs after alloxan	221.13 ± 4.83	221 ± 4.93	222 ± 4.76	221 ± 4.76	**0.98**
Repeat Measures ANOVA applied between groups (p<0.05 taken as significant)					

Table 4: S.Insulin levels (µ IU/ml) after alloxan 140 mg/kg

S. Insulin (µ IU/ml, MEAN ± SD)					
	GR- I	**GR- II**	**GR - III**	**GR - IV**	**p value**
Baseline	3.84 ± 0.15	3.78 ± 0.18	3.74 ± 0.10	3.79 ± 0.09	**0.65**
48 hrs after alloxan	1.80 ± 0.11	1.81 ± 0.10	1.80 ± 0.12	1.83 ± 0.10	**0.8**
Repeat Measures ANOVA applied between groups (p<0.05 taken as significant)					

These values of FBS and S.Insulin attained after induction were used as baseline values for further comparisons in groups I, II, III and IV.

Effect of Gatifloxacin Alone On FBS Levels In Diabetic (Group III) And Non-Diabetic (Group V) Rabbits

FBS at baseline, after 1 week and after 2 weeks of gatifloxacin medication in diabetic rabbits was estimated.

The difference in FBS level before and after gatifloxacin medication was statistically insignificant (p=0.45). (Table 5).

Table 5: FBS (mg/dl) After 2 Weeks of Gatifloxacin Medication In Group III

Variation in FBS (mg/dl, MEAN ± SD) in Group III				
	Baseline (induction)	**1 week**	**2 weeks**	**p value**
FBS (mg/dl)	222 ± 4.76	220.75 ± 3.71	220.38 ± 3.52	**0.45**
Repeat Measures ANOVA applied within group (p<0.05 taken as significant)				

FBS at baseline, after 1 week and after 2 weeks of gatifloxacin medication in non-diabetic rabbits was estimated. The difference in FBS level before and after study medication was statistically insignificant (p=0.64). (Table 6).

Table 6: FBS (mg/dl) after 2 weeks of gatifloxacin medication in group v

Variation in FBS (mg/dl, MEAN ± SD) in Group V				
	Baseline	**1 week**	**2 weeks**	**p value**
FBS (mg/dl)	93.63 ± 2.92	93.25 ± 2.71	93.38 ± 2.74	**0.64**
Repeat Measures ANOVA applied within group (p<0.05 taken as significant)				

Effect of Gatifloxacin medication on S. Insulin levels in diabetic (Group III) and non-diabetic (Group V) rabbits
S. Insulin at baseline, after 1 week and after 2 weeks of gatifloxacin medication in diabetic rabbits was estimated. (Table 7).

Table 7: S. Insulin (µ IU/ml) after 2 weeks of Gatifloxacin medication in Group III

Variation in S. Insulin (µ IU/ml, MEAN ± SD) in Group III				
	Baseline (induction)	**1 week**	**2 weeks**	**p value**
S. I. (µ IU/ml)	1.80 ± 0.12	1.82 ± 0.10	1.84 ± 0.13	**< 0.001**
Repeat Measures ANOVA applied within group (p<0.05 taken as significant)				

S. Insulin at baseline, after 1 week and after 2 weeks of gatifloxacin medication in non-diabetic rabbits. (Table 8).

Table 8: S. Insulin (µ IU/ml) after 2 weeks of Gatifloxacin medication in Group V

Variation in S. Insulin (µ IU/ml, MEAN ± SD) in Group V				
	Baseline	**1 week**	**2 weeks**	**p value**
S. I. (µ IU/ml)	3.76 ± 0.12	3.77 ± 0.11	3.78 ± 0.14	**0.93**
Repeat Measures ANOVA applied within group (p<0.05 taken as significant)				

EFFECT OF CONTROL AND STUDY MEDICATIONS ON FBS LEVELS IN DIABETIC RABBITS (GROUPS I, II, III AND IV)
Comparison of FBS levels, within groups, at start and end of study
Change in FBS values in the diabetic rabbits at different stages of therapy are given below. (Table 9).

Table 9: Effect of control and study medications on FBS levels (mg/dl) in diabetic rabbits

Variation in FBS(mg/dl, MEAN ± SD) throughout therapy				
	GR- I	**GR- II**	**GR – III**	**GR – IV**
48 hrs after alloxan	221.13 ± 4.83	221 ± 4.93	222 ± 4.76	221 ± 4.76
After I week therapy	220.38 ± 3.52	197.38 ± 3.74	220.75 ± 3.71	197.25 ± 3.71
After 2 weeks therapy	219.88 ± 3.64	177.88 ± 3.83	220.38 ± 3.52	178 ± 3.76
p value	**0.09**	**< 0.001**	**0.45**	**< 0.001**
Repeat Measures ANOVA applied within groups (p<0.05 taken as significant)				

Comparison of FBS levels, between GR- I & GR- III at 1 and 2 weeks
At the end of 1 and 2 weeks of therapy, reduction in the FBS level in the control treated group was statistically insignificant as compared to the group treated with Gatifloxacin (Table 10).

Table 10: Comparison of FBS (mg/dl) between GR- I & GR- III, at 1 and 2 weeks

Comparison of FBS(mg/dl, MEAN ± SD) between GR- I & GR- III			
	GR- I	**GR - III**	**p value**
At end of 1 week	220.38 ± 3.52	220.75 ± 3.71	**0.25**
At end of 2 week	219.88 ± 3.64	220.38 ± 3.52	**0.11**
Unpaired 't'-Test applied between groups (p<0.05 taken as significant)			

Comparison of FBS levels, between GR II & GR III, at 1 and 2 weeks
At the end of 1 and 2 weeks of therapy, the reduction in the FBS level in the glyburide treated group was statistically significant as compared to the group treated with gatifloxacin (table 11).

Table 11: Comparison of FBS (mg/dl) between GR II & GR III, at 1 and 2 weeks

Comparison Of FBS(mg/dl, MEAN ± SD) between GR II & GR III			
	GR- II	**GR - III**	**p value**
At end of 1 week	197.38 ± 3.74	220.75 ± 3.71	**< 0.001**
At end of 2 week	177.88 ± 3.83	220.38 ± 3.52	**< 0.0001**
Unpaired 't'-Test applied between groups (p<0.05 taken as significant)			

Comparison of FBS levels, between GR III & GR IV, at 1 and 2 weeks

At the end of 1 and 2 weeks of therapy, the reduction in the FBS level in the group treated with combination of glyburide and gatifloxacin was statistically significant as compared to the group treated with gatifloxacin alone (Table 12).

Table 12: Comparison of FBS (mg/dl) between GR III & GR IV, at 1 and 2 weeks

Comparison of FBS(mg/dl, MEAN ± SD) between GR III & GR IV			
	GR- III	**GR - IV**	**p value**
At end of 1 week	220.75 ± 3.71	197.25 ± 3.71	**<0.001**
At end of 2 week	220.38 ± 3.52	178 ± 3.76	**<0.0001**
Unpaired 't'-Test applied between groups. (p<0.05 taken as significant)			

Comparison of FBS levels, between GR II & GR IV, at 1 and 2 weeks

At the end of 1 and 2 weeks of therapy, the reduction in the FBS level in the glyburide treated group was statistically insignificant as compared to the group treated with a combination of glyburide and gatifloxacin (Table no. 13).

Table 13: Comparison of FBS (mg/dl) between GR II & GR IV, at 1 and 2 weeks

Comparison of FBS(mg/dl, MEAN ± SD) between GR II & GR IV			
	GR- II	**GR - IV**	**p value**
At end of 1 week	197.38 ± 3.74	197.25 ± 3.71	**0.74**
At end of 2 week	177.88 ± 3.83	178 ± 3.76	**0.76**
Unpaired 't'-Test applied between groups (p<0.05 taken as significant)			

EFFECT OF CONTROL AND STUDY MEDICATIONS ON S. INSULIN LEVELS IN DIABETIC RABBITS GROUPS I, II, III & IV

Change in S. Insulin values in the diabetic rabbits at different stages of therapy are given below. (Table 14).

Comparison of S. Insulin levels, within groups, at start and end of study

Table 14: Effect of control and study medications on S. I. Levels (µ IU/ml) in diabetic rabbits

Variation in S. I. (µ IU/ml, MEAN ± SD) throughout therapy				
	GR- I	**GR- II**	**GR - III**	**GR - IV**
48 hrs after alloxan	1.80 ± 0.11	1.81 ± 0.10	1.80 ± 0.12	1.80 ± 0.10
After I week therapy	1.83 ± 0.12	2.32 ± 0.10	1.82 ± 0.10	2.38 ± 0.14
After 2 weeks therapy	1.85 ± 0.11	2.56 ± 0.10	1.84 ± 0.13	2.56 ± 0.14
p value	**< 0.001**	**< 0.0001**	**< 0.001**	**< 0.0001**
Repeat Measures ANOVA within groups (p<0.05 taken as significant)				

Effect of control and study medications on S. Insulin levels in diabetic rabbits (Groups I, II, III & IV)

Comparison of S. Insulin levels, between gr- i & gr iii, at 1 and 2 weeks

At the end of 1 and 2 weeks of therapy, the rise in the S. Insulin level in the control treated group was statistically insignificant as compared to the group treated with gatifloxacin (Table 15).

Table 15: Comparison of S. I. (µ IU/ml) between Group I & III, at 1 and 2 weeks

Comparison of S. I. (µ IU/ml, MEAN ± SD) between Group I & III			
	GR- I	**GR - III**	**p value**
At end of 1 week	1.83 ± 0.12	1.82 ± 0.10	**0.64**
At end of 2 week	1.85 ± 0.11	1.84 ± 0.13	**0.99**
Unpaired 't'-Test applied between groups (p<0.05 taken as significant)			

Comparison of S. Insulin levels, between Group II & III, at 1 and 2 weeks

At the end of 1 and 2 weeks of therapy, the rise in the S. Insulin level in the glyburide treated group was statistically significant as compared to the group treated with gatifloxacin (Table 16).

Table 16: Comparison of S. Insulin (µ IU/ml) between Group II & III, at 1 and 2 weeks

Comparison of S. I. (µ IU/ml, MEAN ± SD) between Group II & III			
	GR- II	**GR - III**	**p value**
At end of 1 week	2.32 ± 0.10	1.82 ± 0.10	**< 0.0001**
At end of 2 week	2.56 ± 0.10	1.84 ± 0.13	**< 0.0001**
Unpaired 't'-Test applied between groups (p<0.05 taken as significant)			

Comparison of S. Insulin levels, between Group III & IV, at 1 and 2 weeks

At the end of 1 and 2 weeks of therapy, the rise in the S. Insulin level in the group treated with combination of glyburide and gatifloxacin was statistically significant as compared to the group treated with gatifloxacin alone (Table 17).

Table 17: Comparison of S. Insulin (µ IU/ml) between Group III & IV, at 1 and 2 weeks

Comparison of S. I. (µ IU/ml,MEAN ± SD) between Group III & IV			
	GR- III	**GR - IV**	**p value**
At end of 1 week	1.82 ± 0.10	2.38 ± 0.14	**<0.001**
At end of 2 week	1.84 ± 0.13	2.56 ± 0.14	**<0.0001**
Unpaired 't'-Test applied between groups (p<0.05 taken as significant)			

Comparison of S. Insulin levels, between Group II & IV, at 1 and 2 weeks

At the end of 1 and 2 weeks of therapy, the rise in S. Insulin level in the glyburide treated group was statistically insignificant as compared to the group treated with a combination of glyburide and gatifloxacin (Table 18).

Table 18: Comparison of S. Insulin (µ IU/ml) between Group II & IV, at 1 and 2 weeks

Comparison of S. I. (µ IU/ml, MEAN ± SD) between Group II & IV			
	GR- II	**GR - IV**	**p value**
At end of 1 week	2.32 ± 0.10	2.38 ± 0.14	**0.59**
At end of 2 week	2.56 ± 0.10	2.56 ± 0.14	**1**
Unpaired 't'-Test applied between groups (p<0.05 taken as significant)			

Effects of control and study medications on safety parameters

Body weight

The body weight from baseline to the end of treatment period (i.e. 2 weeks) was estimated. At baseline all the groups were comparable for body weight (p=0.19). (Table 19).

Table 19: Comparison of body weight (kg) before and after completion of study

Body weight (Kg, MEAN ± SD)					
	GR- I	**GR- II**	**GR - III**	**GR - IV**	**GR - V**
Baseline	1.93 ± 0.02	1.93 ± 0.01	1.93 ± 0.05	1.93 ± 0.01	1.92 ± 0.01
After 2 weeks	1.91 ± 0.01	1.94 ± 0.01	1.92 ± 0.01	1.94 ± 0.01	1.93 ± 0.01
p value	**0.009**	**0.007**	**0.007**	**0.001**	**0.0002**
Paired 't' test applied within groups (p<0.05 taken as significant)					

OBSERVATION AND DISCUSSION

The non-diabetic animals, fed with oral gatifloxacin (group V) alone for 2 weeks, showed no significant changes in FBS levels when compared to the baseline values (p=0.64). Similarly, the S. Insulin levels, in this group, rose marginally but the change was found to be insignificant (p=0.93). This showed that gatifloxacin, on prolonged treatment, produced no significant changes in FBS and S. Insulin levels, in non-diabetics. The body weight of these animals increased significantly (p=0.0002) over the treatment period.

In the animals fed with control medication (group I) for 2 weeks, the FBS levels reduced marginally from baseline induction value (1.25 mg/dl) and this reduction was insignificant (p=0.09). There was a marginal rise in S. insulin level (0.05 µ IU/ml) which was however found to be significant (p<0.001). Improvement in FBS and S. insulin levels seen in this group was probably due to spontaneous recovery of some β – islet cells damaged by alloxan. The body weight of the animals in this group were seen to reduce significantly (p=0.009) probably due to the untreated hyperglycemia induced metabolic changes.

In the animals fed with oral glyburide (group II) alone for 2 weeks, the FBS levels reduced markedly (43.12 mg/dl) and this reduction was significant (p<0.001). This was associated with a marked rise in S. insulin level (0.75 µ IU/ml) which was also found to be significant (p<0.0001). Improvement in FBS and S. insulin levels seen in this group was due to glyburide being

administered to the animals. It well known that glyburide brings about reduction in blood glucose levels by stimulating the release of insulin by degranulation of β-islet cells of pancreas.[19,20] The body weight of the animals in this group were seen to rise significantly (p=0.007) due to glyburide medication for the hyperglycemic state.[20,21,22]

In the animals fed with oral gatifloxacin (group III) alone for 2 weeks, the FBS levels reduced marginally (2.38 mg/dl) and this reduction was insignificant (p=0.45). There was a marginal rise in S. insulin level (0.04 µ IU/ml) which was however found to be significant (p<0.001). These marginal improvements in FBS and S. insulin levels seen in this group was probably due to spontaneous recovery of some β-islet cells damaged by alloxan. The body weight of the animals in this group were seen to reduce significantly (p=0.007) probably due to the untreated pathological course of metabolic changes following hyperglycemic state.

On comparison, the difference in FBS and S. Insulin levels between group I and group III, at the end of 2 weeks were found to be insignificant (p=0.11; p=0.99 respectively). This showed that on prolonged therapy with gatifloxacin there was no significant drop in FBS levels compared to that after control medication, in diabetics.

However, on comparing the FBS and S. Insulin levels between group II and group III, at the end of 2 weeks, there was a significant difference in the values (p<0.0001 for both values). This showed that gatifloxacin, on prolonged treatment, has a lesser chance of producing decrease in FBS levels and this drop in FBS levels was much less compared to a known hypoglycemic agent, i.e. glyburide used in this study.

In the animals fed with combination of oral glyburide and gatifloxacin (group IV), the FBS levels reduced markedly (43 mg/dl) and this reduction was significant (p<0.001). This was associated with a marked rise in S. insulin level (0.73 µ IU/ml) which was also found to be significant (p<0.0001). Improvement in FBS and S. insulin levels seen in this group was due to glyburide medication being administered.[19,20] The body weight of the animals in this group were seen to rise significantly (p=0.001) due to glyburide medication[20,21,22] for the hyperglycemic state.

CONCLUSIONS

Gatifloxacin, at therapeutic doses, had no effect on blood glucose levels or insulin release from pancreas, even on prolonged intake, both in diabetics and non-diabetics. Concurrent administration of gatifloxacin and glyburide did not significantly reduce blood glucose concentrations, than when glyburide is administered alone, in diabetics. Oral gatifloxacin has no effect on the normal functioning of liver and kidneys. We may therefore conclude that gatifloxacin should be avoided as an outpatient or as an over the counter drug. It may, be used on an inpatient basis as the recipient is under medical observation. Any changes in blood sugar levels can be detected at the earliest and corrective measures can be taken. However, drawing any direct conclusions from this study for application to a clinical state would not be appropriate. But for the moment, as clinical reports regarding gatifloxacin stand, and the results obtained following this particular experimental study, the drug must be used with utmost caution, even probably reduce the dose to half (i.e. 200mg instead of 400 mg once daily) in elderly patients with creatinine clearance < 40 ml/min. Caution needs to be exercised in diabetics as well as non-diabetics.

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