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A Pharmacodynamic Pilot Study to Evaluate the Effect of Gatifloxacin and Glyburide Alone and in Combination on Plasma Glucose and Serum Insulin Levels in Healthy Human Subjects

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ABSTRACT

Although some drug related problems develop unexpectedly and cannot be predicted, many are related to known pharmacological actions of drugs and reasonably can be anticipated. However, as the drug therapy become more complex and because many patients are being treated with two or more drugs, the ability to predict the magnitude of a specific action of any given drug diminishes. These circumstances require not only maintenance of complete and current medications records for patients, but also for closer monitoring and supervision of the drug therapy so that problems could be prevented or detected at an early stage in the treatment. The dearth of reports on glyburide-gatifloxacin interaction leading to hypoglycemia is surprising, given rather broad use of both these drugs. There have been rare postmarketting reports of hypoglycemia in patient's concurrently taking glyburide and gatifloxacin. Possibly, hypoglycemia may be inadvertently attributed solely to glyburide, either because concomitant use of both the medicines is not well documented, or because of lack of appreciation of possibility of such a reaction by medical professionals. In the present study, accordingly, case reports served as a stimulus to evaluate the effects of gatifloxacin and glyburide alone and in combination on plasma glucose and serum insulin levels in healthy, adult, male, human volunteers and to assess the safety and tolerability of concomitant administration. The results of the study indicated that gatifloxacin when given alone or in combination with glyburide had influence on plasma glucose and serum insulin levels in time specific manner. The effect did result in significant oscillations in plasma glucose and serum insulin levels.

KEYWORDS: Gatifloxacin, Glyburide, Serum Insulin, Plasma Glucose

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INTRODUCTION

Diabetes mellitus is all set to become the first major epidemic of the millennium. There are about 150 million sufferers worldwide and the prevalence is rising. The global prevalence of diabetes is expected to double by the period 2000-25 and may reach a level of almost 300 million. In India alone, 35 million people have been diagnosed with diabetes and an estimated additional 7.5 million have undiagnosed diabetes. With these alarming statistics, India is emerging as a "Diabetic Capital" of the world in not so distant future.

The findings of the DCCT, UKPDS, and Kumamoto study have proven that chronic and substantial elevation of circulating glucose plays a causative role in the pathogenesis of diabetic complications. These landmark studies have established the importance of intensive glycemic control in all forms of diabetes. It is now well established fact that patients with poorly controlled diabetes are more susceptible to infections, including, upper respiratory tract, skin and soft tissue and urinary tract infections and gatifloxacin a new fluoroquinolone with its broad spectrum of coverage, and once daily dosing, has proven to be an excellent treatment option. Because of its proved clinical efficacy in variety of clinical infection, its potential effect in individual with non-infectious morbidities is worthy of investigation. [1-4]

Though, drug interactions between the fluoroquinolones and the oral hypoglycemic agents are not listed in the prescribing information of the fluoroquinolones or in the standard textbook. However, more recently fluoroquinolone associated alterations in glucose homeostasis has got increased attention, because of more frequently reported cases of its effect leading to on glucose homeostasis abnormality. Of particular concern are patients with type 2 diabetes, who are taking oral hypoglycemic agents and prone to variety of infections, and in whom other fluoroquinolones have demonstrated effects on glucose homeostasis.

However, published clinical reports represents only the tip of an enormous iceberg, and it is particularly difficult to know how often concomitant administration of gatifloxacin and glyburide, an oral sulfonylureas are responsible for effect on glucose homeostasis abnormality. Though, many drug interactions are reported as case reports, but most of them are not substantiated by other observations or additional study. Many a times single-case report has served as a stimulus for additional studies that has resulted in warnings about potentially dangerous drug interactions.[5-8]

MATERIAL AND METHODS

The study was performed as an open label, randomized, three way parallel study and the experimental design of the study was divided into three parts: Clinical, Analytical and the Statistical analysis.

CLINICAL METHODOLOGY

The study was carried out in accordance with the ethical principles that have their origins in the principles defined in US 21 CFR Part 312.20, the ICH (62FR25692, 09 may 1997) 'Good Clinical Practice (GCP) for Trials on Pharmaceutical Products', and the principles enunciated in the Declaration of Helsinki (Edinburgh, October 2000). Protocol and corresponding Inform Consent Form (ICF) used to obtain consent of the study volunteers were reviewed by the Jamia Hamdard Institutional Review Board (JHIRB).

The required healthy human volunteers were selected on the basis of screening criteria, inclusion (age range of 18-45 years, Neither overweight nor underweight as per the Life Insurance Corporation of India height/weight chart of normal health as determined by medical history and physical examination performed within 21 days prior to the commencement of the study), and exclusion criteria (Subjects with history of allergy or hypersensitivity to gatifloxacin or glyburide or related compounds or whom have QT prolongation or the disease/condition predisposing to QT prolongation were excluded)

Twenty four healthy volunteers were selected from the volunteer bank of Clinical Pharmacology Unit and subjects were randomized according to SAS-generated randomization schedule to receive one of the three treatments Treatment A: Gatifloxacin 400 mg, Treatment B: Glyburide 5 mg and Treatment C: Gatifloxacin 400 mg and Glyburide 5 mg. Volunteers were admitted and in-housed in the Clinical Pharmacology Unit from 12 hours before drug administration and sampling and were discharged after 24 hours of dosing on day-07, if the volunteers did not suffered from any adverse drug reaction. After an overnight fast of 10 to 12 hours, volunteers were dosed as per randomization schedule. All volunteers were asked to fast overnight for at least 10 to 12 hours before dosing. They received standard meals throughout the duration of study. A total of 14 blood samples (7 mL each, 2 mL for plasma glucose and 5 mL for serum insulin) were collected during the study and the blood loss for each volunteer. Blood Sampling was done predose and postdose at 1, 2, 4, 6, 12, 24 hours on day 1 & 7.

Clinical examination of the volunteer was conducted by a qualified medical designate on duty after volunteer admission, prior to dosing of drug and during the course of study every 12 hourly. The vital signs of oral temperature, sitting blood pressure, and radial pulse were measured prior to drug

administration on all study days and before discharge. Volunteers were monitored throughout the study for adverse events. They were specifically asked about adverse events on all the study days. Volunteers were also advised to promptly report in case they have increase in heart rate, sweating, palpitations, tremor, headache, confusion, visual disturbances, irritability to the medical Officer/Nurse/Staff on duty.

ANALYTICAL METHODOLOGY

Blood samples were collected in 2ml vacutainer containing sodium fluoride, Sodium EDTA as anticoagulant for plasma glucose estimation and 5 ml vacutainer containing SST Gel and clot activator for serum Insulin estimation. Estimation of plasma glucose level was performed on the dimension clinical chemistry system after the method was validated and instrument was calibrated. The GLU flex reagent cartridge was required to perform the GLU test. Sampling, reagent deliver, mixing, processing and printing of the results were automatically performed by Dimension system.Reference range for plasma glucose level was Fasting plasma glucose levels 70-110 mg/dl and Random plasma glucose levels 100-130 mg/dl. Immunoenzymometric assay method was used for the quantitive measurement of insulin in serum. Medgenix Ins-Easia Kit was used for the quantitative determination of insulin levels in human serum. The Reference range for serum insulin level taken was 2 to 25 μIU/ml

STATISTICAL METHODOLOGY

Repeated measure analysis of co-variance was performed to analyze plasma glucose and serum insulin level data on each study day (i.e. Day-1 and Day-7). Sampling hour (1, 2, 4, 6, 12, 24) was treated as repeating factor in the model. Baseline predose value was assumed to be as covariate. In case treatment and time point interaction was significant, then follow-up was done by using two-sample t-test at each sampling time point. All the statistical analysis was performed using Proc Mixed SAS 9.1.2 (SAS Institute INC. Cary NC, USA). Alpha level was set 5% two sided for statistical significance.

STUDY DOCUMENTATION

All data generated during the conduct of the study was directly entered in the case report form and later transcribed into the study related forms.

RESULTS AND DISCUSSION

24 subjects started the study and 22 subjects successfully completed [One subject was withdrawn (Adverse event) from the study and one subject dropped out on account of loss of interest]. Subjects were ranged in age from 19-33 yrs with mean $\pm$ SD age of 24.83 $\pm$ 4.41, body weight ranged from 47-68 kg with mean $\pm$ SD weight of 55.16 $\pm$ 6.25 and height ranged from 152-184 cm with mean $\pm$ SD height of 168.54 $\pm$ 6.41.

A total of forty two (42) non serious adverse events were reported during the course of the study. Nineteen (19) adverse events (Treatment A: 4; Treatment B: 6; Treatment C: 9) of dizziness, Twelve (11) adverse events (Treatment A: 3; Treatment B: 3; Treatment C: 5) of sweating, palpitations and visual disturbances, Three (03) adverse events (Treatment A: 1; Treatment C: 2) of headache, One (01) adverse event (Treatment C) of nausea, One (01) adverse event (Treatment: A) of heart burn, One (01) adverse event (Treatment: C) of pain abdomen, One (01) adverse event (treatment: A) of high B.P was reported during the study. Five (05) adverse event (treatment: A) of dryness of the mouth and alteration in the taste were reported during the study. All events reported were mild to moderate in intensity and the events recovered without sequelae.

The effect of treatments on plasma glucose level and serum insulin levels were compared with each other on day-1 and on day-7 (Fig-1 to 6, Table-1 and 2) of the study and it was found that hour and hour * treatment interaction was statistically significant (p-value less than 0.05) indicating that the differences among the treatments were not consistent among sampling hours and study days. The effect of treatments on serum insulin levels on day-1 and day-7 followed a same trend line; with significant effect on serum insulin levels observed with gatifloxacin alone (Fig-6, Table-2).

In healthy individuals, a normal plasma glucose level is needed to maintain physiological functions and meet the energy needs of the brain and various tissues. Insulin secretion decreases as plasma glucose level falls. Hypoglycemia and hyperglycemia both result from an imbalance between plasma glucose and insulin levels.

Many drugs and their combination are known to induce hypo- or hyperglycemia through a variety of mechanisms, including alterations of insulin secretion and sensitivity, changes in gluconeogenesis, and direct cytotoxic effects on pancreatic beta cells. Drug-induced hypo- or hyperglycemia can lead to significant consequences. However, these events can be prevented and/or minimized with awareness of the problem, close monitoring, and judicious use of the suspect drug(s).
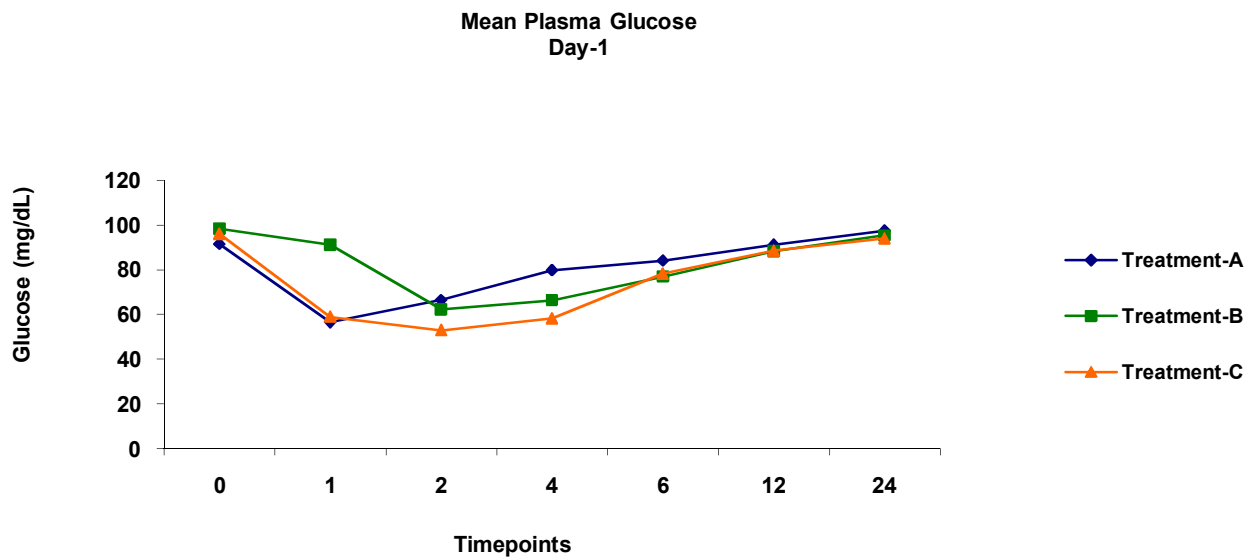
**Mean Plasma Glucose
Day-1**

Figure 1: Mean plasma glucose levels till 24 hours post dose day-1
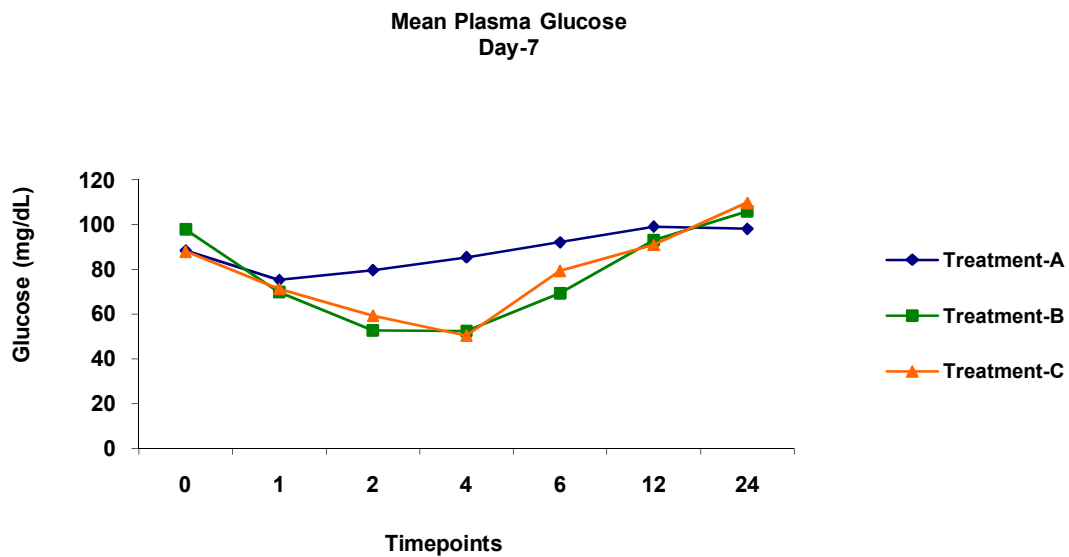
**Mean Plasma Glucose
Day-7**

Figure 2: Mean plasma glucose levels till 24 hours post dose day-7

Table No. 1 Treatment Comparison Plasma Glucose Levels

Treatment Comparisons	1hr	2hr	4hr	6hr	12hr	24hr
Day-1						
Treatment A Vs B	0.0001*	0.5700	0.0474*	0.3533	0.7406	0.5246
Treatment A Vs C	0.7128	0.1033	0.0003*	0.5671	0.9006	0.3559
Treatment B Vs C	0.0009*	0.0299*	0.2495	0.9066	0.9765	0.7255
Day-7						
Treatment A Vs B	0.6755	0.0074*	0.0005*	0.0349*	0.4877	0.0977
Treatment A Vs C	0.7926	0.0426*	0.0003*	0.0663	0.4270	0.0351*
Treatment B Vs C	0.9099	0.5299	0.7944	0.6202	0.8810	0.4578

@ Hour* Treatment interaction was significant.

*P-value less than 0.05 were considered to be statistically significant.

Table No. 2 Treatment Comparison Serum Insulin Levels

Treatment Comparisons	1hr	2hr	4hr	6hr	12hr	24hr
Day-1						
Treatment A Vs B	0.0333*	0.0292*	0.2644	0.0203*	0.4214	0.8210
Treatment A Vs C	0.0133*	0.0206*	0.0180*	0.0326*	0.2563	0.4050
Treatment B Vs C	0.9090	0.4725	0.2775	0.3433	0.7512	0.3997
DAY-7						
Treatment A Vs B	0.0485*	0.0632	0.0812	0.1147	0.2288	0.8492
Treatment A Vs C	0.0208*	0.0805*	0.0350*	0.0381*	0.2278	0.1478
Treatment B Vs C	0.4011	0.6974	0.3420	0.0481*	0.7940	0.1338

@ Hour* Treatment interaction was significant.

*P-value less than 0.05 were considered to be statistically significant.
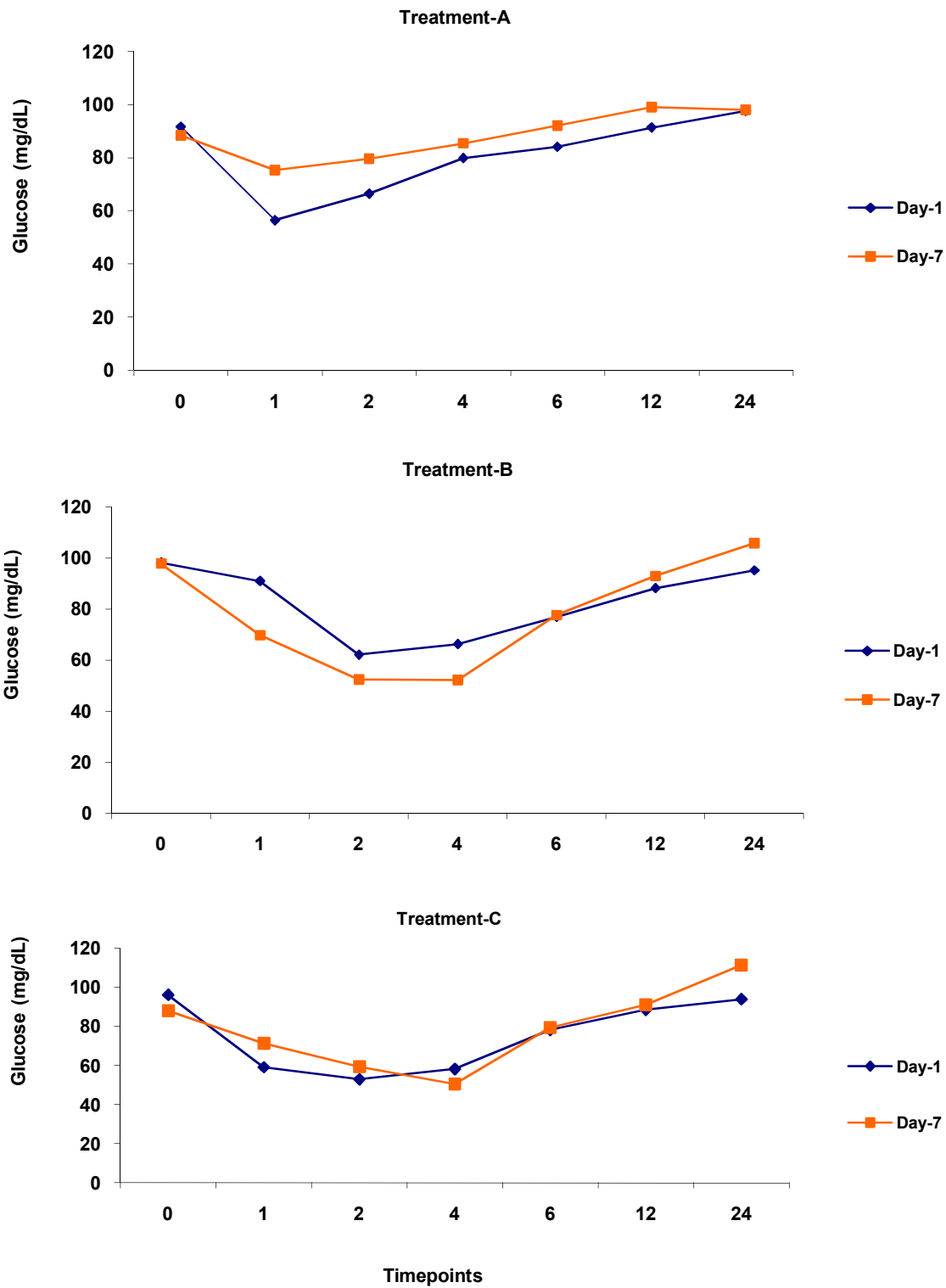
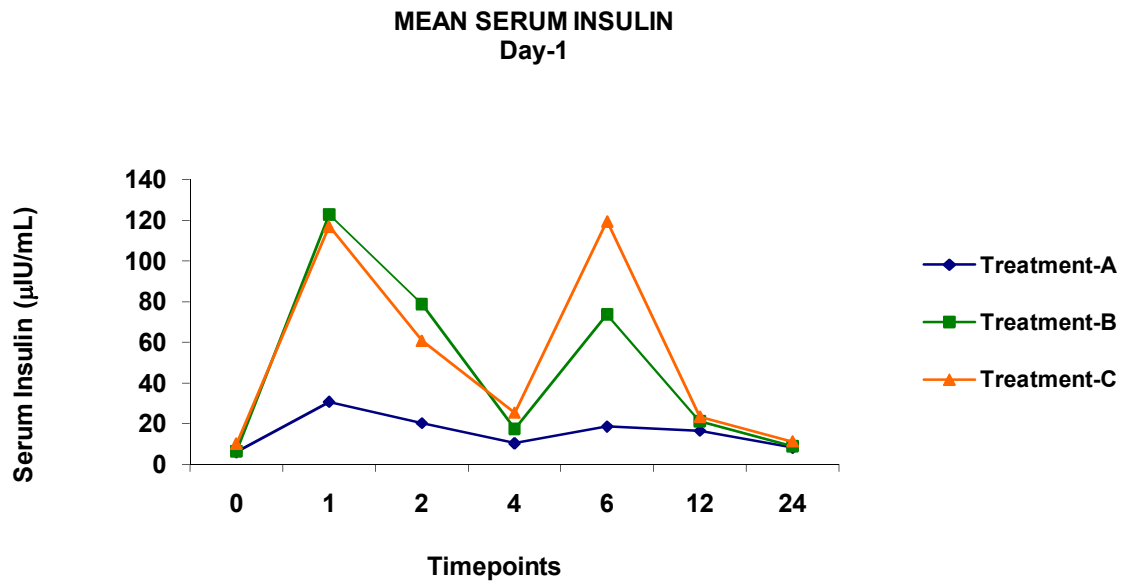**Figure 3: Plasma glucose level comparison between day-1 and day-7 of the study.**

MEAN SERUM INSULIN
Day-1

Figure 4:Mean serum insulin levels till 24 hours post dose on day-1

MEAN SERUM INSULIN
Day-7
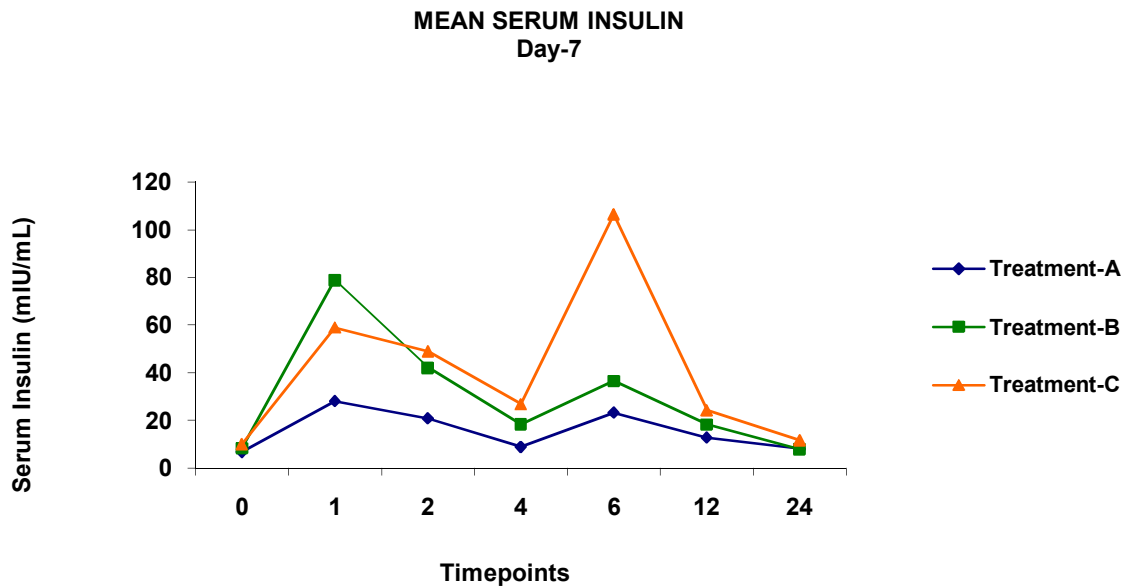
Figure 5: Mean serum insulin levels till 24 hours post dose day-07

Treatment-A

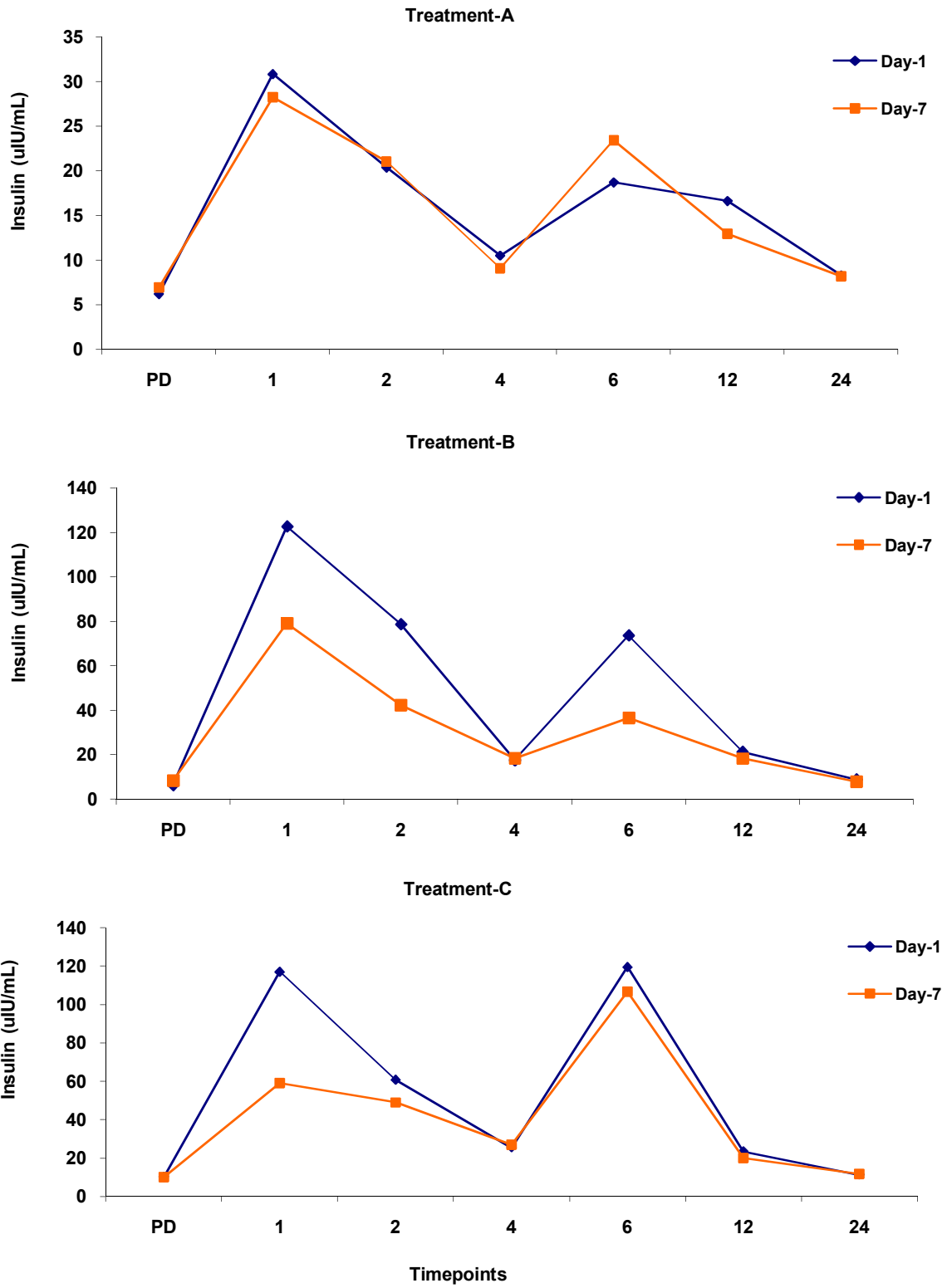**Treatment-B**

Treatment-C

Figure 6: Serum insulin level comparison between day-1 and day-7 of the study.

The adverse consequences of hypo- and hyperglycemia now have gained attention within the health care community. There is growing body of literature documenting the increased complication rates, in patients with short- and long-term hyperglycemia. However, with the increased focus on tight glycemic control an increased incidence of drug-induced hypoglycemia occurs.

The data on the incidence of glucose homeostasis abnormalities with specific fluoroquinolones are imperfect because they are based mainly on spontaneous reporting that is often subject to underreporting, and there is also the possibility that there has been ascertainment bias in the cases of gatifloxacin. However, each reports represents a suspicion, opinion or observation of the individual reporter and such case reports are good enough to generate signals of potential health product safety issues during the post-marketing period. However, more recently fluoroquinolone associated alterations in glucose homeostasis has got increased attention, despite many years of fluoroquinolones use in more than 500 million patients.

Accumulated case reports however cannot be used as a basis for determining the incidence of a reaction or estimating risk for a particular product as neither the total number of reactions occurring, nor the number of patients exposed to the health product is known. The present study therefore was planned on the basis of these case reports to characterize the effects of gatifloxacin and glyburide alone and in combination on plasma glucose and serum insulin levels.

This study was carried out in accordance with the Basic Principles defined in US 21 CFR Part 312.20, the ICH 'Good Clinical Practice' and the principles enunciated in the Declaration of Helsinki. During the clinical conduct of the study, a total of 24 subjects were enrolled for the study and 22 subjects successfully completed the study. The study treatments were well tolerated by the study subjects.

Administration of gatifloxacin for 7 days did not significantly affect the plasma glucose level. However, it resulted in modest, transient increase in serum insulin levels 1 hour after dose on day-1 and day-7. The combination of gatifloxacin and glyburide had more profound affect on glucose homeostasis. This effect did result in significant alterations in plasma glucose and serum insulin levels, both increase and decrease in plasma glucose levels was observed from the reference range. But it was not maintained throughout the time period. Both the treatment demonstrated effect on glucose homeostasis in time specific manner.

Decrease in plasma glucose levels than the normal reference range appeared to be due to an increase in insulin release from the pancreas. Gatifloxacin increases insulin release by blocking the K^+-ATP channels on the ß-islet cell membranes. This is also a class effect of fluoroquinolones. In the present study, gatifloxacin was found to increase serum insulin levels 1-hour after a dose, but this did not had a significant effect after that; there was no effect on blood glucose levels. The magnitude of insulin

release following a dose of gatifloxacin decreased with subsequent doses. This may in part explains why hypoglycemia tends to occur earlier in the treatment course. It is quite possible that for glucose homeostasis abnormality to occur in the elderly is by the fact that they experience an age-related decline in renal function and usually has significantly higher serum concentrations of renally excreted drugs compared with younger adults. Since gatifloxacin is renally excreted, higher serum concentrations will be achieved in the elderly and this will likely increase the risk of glucose homeostasis abnormality.

However, the mechanism for increase in plasma glucose level over a period of 7 days and at 24 hour sampling is still unknown, and is unclear. May be it is due to a direct drug effect on glucose metabolism or is a differential effect of fluoroquinolones. In our study subjects were healthy in all respects and it is a well-known fact that the presence of an infection may stimulate a hyperglycemic episode in known diabetics. Therefore, hyperglycemia during fluoroquinolones therapy may be a function of a disease state effect and not related to a direct drug effect.

A differential effect of individual fluoroquinolones on glucose homeostasis abnormalities is supported by experimental animal data as well. However, in animals given higher than normal doses of a fluoroquinolone, there were decreased secretory granules found in the pancreatic ß-cells after prolonged dosing. This resulted in decreased serum insulin levels with a reciprocal increase in glucose levels. One may postulate that this same effect could be seen in humans with high serum concentrations of a fluoroquinolone for a long period of time. This could possibly explain the findings of hyperglycemia tending to occur later in a course of therapy.[9-11]

The critical question is what this all means for clinical practice, given that the absolute incidence of glucose homeostasis abnormality is quite low, even with gatifloxacin. Our's Believe is that there are 3 possible approaches. One is to avoid gatifloxacin altogether, although it has been demonstrated to be superior to other fluoroquinolones for any indication. A second approach is to avoid gatifloxacin in diabetic patients receiving oral hypoglycemic therapy. The third approach is to avoid gatifloxacin in all diabetic patients regardless of whether the patient is receiving oral hypoglycemic therapy or not. The latter 2 approaches will reduce the risk of hypoglycemia in diabetic patients, but won't avoid the possibility of hyperglycemia in nondiabetic patients.

On the whole, the results of the present study indicate that there exist some significant effect of gatifloxacin and glyburide in combination on glucose homeostasis leading to hypo- and hyperglycemia. The results are in agreement with the reported cases, where it was reported that; the fluoroquinolones, gatifloxacin, affects glucose homeostasis leading to both hypo- and hyperglycemia when administered alone or in combination with sulfonylureas, with, preponderance of hypoglycemia.

Although we cannot prove with certainty that the effect on glucose homeostasis by the combination group was caused by additive effect of gatifloxacin or was the sole effect of glyburide, a search for other possible etiologies was not possible.

CONCLUSION

The present study concluded that the 7 days treatment with gatifloxacin at a dose usually recommended 400 mg/day when given alone or in combination with glyburide 5 mg/day had influence on plasma glucose and serum insulin levels in time specific manner. The effect did result in significant variations in plasma glucose and serum insulin levels. During the study six volunteers taking gatifloxacin alone or in combination reported hypoglycemic signs and symptoms, which indicated that the effect was clinically significant.

Further, clinicians should become aware of the glucose altering effects of gatifloxacin, when prescribing gatifloxacin for patient receiving oral hypoglycemic agents. Patients with type 2 diabetes receiving oral hypoglycemic agents such as oral sulfonylureas may be at a greater risk than those not receiving these agents. Blood glucose levels should be monitored closely during the early phase of treatment, to detect development of hypoglycemia. During later phase of therapy, signs and symptoms of hyperglycemia should be monitored. If signs and symptoms occur in any patient receiving gatifloxacin, the antibiotic to be discontinued immediately.

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