Study of Adverse Effects of Vildagliptin and Insulin Treatment in Diabetes Mellitus Patients

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Abstract

The defective response of the body tissues to insulin leads to Diabetic condition in human beings. The central nervous system which controls the entire motor unit, suffers degeneration that leads to many complications, of which Diabetes Mellitus disease lies most widespread in India. Present-day medicine such as insulin injection and vildagliptin (Dipeptidyl peptidase-4 inhibitor) treatment are associated with serious neuromuscular side effects and nervous impairment. Within this context, aim of our research was to evaluate, by analysing the myocardial dysfunction complexity, the adverse effects induced by vildagliptin in combination with other antidiabetic treatment. Blood glucose level, glycosylated hemoglobin, serum insulin, systolic and diastolic blood pressure, heart rate, myocardial enzymes such as LDH, CK-MB, AST and ECG signals were measured before and after the insulin and vildagliptin treatment in patients. All the above mentioned parameters were altered significantly after the treatment with insulin and vildagliptin. This study may provide evidence to the medical society about the cardiac dysfunction complexity caused by autonomic failure of hypoglycemic actions upon combination therapy of insulin with vildagliptin in diabetes mellitus.

Keywords: Vildagliptin, Diabetes Mellitus, cardiac markers.

Introduction

Type-2 diabetes mellitus is one of the most challenging non-communicable diseases world wide and will be the most challenging health problems in the 21st century. It has been estimated that the world prevalence of diabetes mellitus in the age groups between 20-79 years will be affecting 439 million adults by 2030[1]. Thus in addition to lifestyle changes effective treatments are also necessary for treating diabetes. So far metformin has been recommended by American diabetes association as a treatment of choice for diabetes mellitus. However underlying pathogenic factors requires additional glucose lowering drugs in addition to it. So the treatment of diabetes has gone towards combining metformin with other drugs with a different mechanism of action. Oral antidiabetic medications can be used in combination with metformin or alone include Dipeptidyl peptidase inhibitors which act by improving Alpha and Beta cell sensitivity to glucose by improving concentrations of active GLP-1[2]. Vildagliptin has been shown to act effectively in combination with metformin[1].

In some cases the patient was found to have low tolerance towards the drug vildagliptin. There are many side effects some of which may include tremors, fatigue, hypoglycemia, blistering of the skin, ulcer in foot, rapid heart rate, low blood pressure and hypotension[2]. The results of the analyses of different DPP-4 inhibitor group of drugs are not entirely comparable but most of them have got deleterious effect on the cardiovascular events[3,4]

The present analyses shows that vildagliptin not only increases the cardiovascular risk but it may produce other side effects also in diabetic patients. The prespecified design of the present analyses included the blinded adjudication of the cardiovascular events which may strengthen the current findings[5]. This analysis was based on individual patient data from a large clinical development programme. This allows derivation of endpoints and minimizes between study heterogeneity of unrelated studies[6].

The present analyses shows that vildagliptin treatment increases cardiovascular risk and may even yield other side effects in patients with type-2 diabetes mellitus. However the prespecified design of the present meta analyses involved prospective and blinded adjudication of cardiovascular events which should strengthen the validity of the current findings[5]. In addition, this meta-analysis was based on individual patient data from a consistently designed, large clinical development programme this allows consistent derivation of endpoints and extensive subgroup analyses and minimizes between study heterogeneity that can confound analyses of unrelated studies[6]. Since, till date, there were no studies have been done on the adverse effect of vildagliptin treatment on cardiovascular dysfunction. Within this context, aim of our research was to evaluate, by analysing the physiological dysfunction complexity, the adverse effects induced by insulin and vildagliptin in human subjects with diabetes. Hence, the present study may helps to understand the progression of cardiovascular adverse effects of insulin and

vildagliptin in diabetic patients taking it as an oral anti diabetic medication by performing various cardiac marker assays.

Material and Methods

A total number of 30 patients were selected from out patient of the diabetic clinic, in India after getting the approval from human ethical clearance. These patients diagnosed as having diabetes mellitus and were under treatment. The patients were selected by the following inclusion critera: under treatment or had diabetes mellitus diagnosed for atleast last one year or more, not having any other systemic diseases and willingness to participate in the study.

In the present study thirty patients with type 2 diabetes subjected to oral hypoglycemic treatments were included. Subjects received insulin at a dose of 20 U, administered twice per day and vildagliptin 50 mg b.i.d. for 90 days in a randomized, double-blind, cross-over design.

At the end of duration of treatment period, blood was collected from the patients and transferred to vacutainers filled with sodium fluoride and serum was separated by centrifugation at 3500rpm for 10min. Fasting blood glucose, Post prandial glucose, AST, CK-MB, LDH, HbA1c and Insulin levels were measured by semi auto analyzer using diagnostic kits. Heart rate, ECG, systolic and diastolic blood pressure was measured by using biomedical devices to analyse the effect of drug on cardiovascular system.

Statistical comparison: All results are presented as means ± SEM. Statistical analysis among subjects was performed by one-way analysis of variance (ANOVA) followed by Dunnett's T3 comparison post-hoc test. Differences were considered statistically significant if $p < 0.05$.

Results and Discussion

Past studies have demonstrated such a strong bond between cardiovascular disease and diabetes, the American heart foundation HA has declared "diabetes is a cardiovascular disease". Diabetes induces complex vascular changes, promoting accelerated atherosclerosis and hypercoagulability, as can be assessed indirectly by a number of markers. Conversely, certain classes of oral antidiabetic medications have been shown to cause hypoglycemia as well as adverse cardiovascular effects[7].

As shown in figure-1 a significant increase in blood glucose and glycosylated hemoglobin and a significant decrease in serum insulin were observed in diabetic patients when compared to normal subjects[8]. Administration of insulin + vildagliptin to diabetic patients significantly decreased the levels of blood glucose and Glycosylated Hb and at same time increased serum insulin[9]. The percentage of patients receiving vildagliptin in combination with insulin and experiencing one or more adverse event, severe adverse event or adverse event leading to discontinuation of the drug. The corresponding percentages for the placebo plus insulin group were 76.9%, 24.4% and 6.4%, respectively[10]. Apart from hypoglycemia, the most common specific adverse event were edema hyperhidrosis, and dizziness[11]. Clinical and observational studies have reported that reducing HbA1c levels results in a lower incidence of cardiovascular complications in diabetic patients with a shorter time since diagnosis[12,13], but not in diabetic patients with a longer time since diagnosis. Starting treatment for diabetes at an earlier stage is therefore thought to be important for decreasing the risk of cardiovascular events[14].

The glucose lowering effect (HbA_{1c} reduction 0.9% from baseline of 7.7%)was in the range seen previously in studies of vildagliptin monotherapy and combination therapy in patients with a much shorter history of type 2 diabetes and normal renal function[15]. As expected, the magnitude of reduction in HbA1c and the between treatment difference was larger in patients with higher baseline HbA1c levels[16]. Thus, the Beta-cell dysfunction and other metabolic derangements attendant with severe renal impairment and longstanding type-2 diabetes requiring insulin therapy clearly did not mitigate the efficacy or the low hypoglycemic potential of vildagliptin[17].

Wide physiological distribution of the Vildagliptin suggests multiple mechanisms of metabolic control, both centrally and through peripheral neurohumoral pathways[18]. In figure-2 studies demonstrate increases in heart rate (HR) and decrease in blood pressure (BP) in insulin + Vildagliptin treated patients compared to normal control. In human studies, few chronotropic and hypotensive effects have been observed in vildalgliptin treated patients which are concordant with our present study. Thus, concomitant mechanisms associated with BP trends seem plausible and are consistent with other findings. Vildalgliptin increased cardiac output and reduced LV end diastolic pressure, in association with improved myocardial insulin sensitivity and myocardial glucose uptake with rapid pacing induced congestive heart failure[19].

Figure-4 shows hypoglycaemia due to the treatment of Vildagliptin alters ventricular repolarization with prolongation of the QT interval, indicating a possible mechanism which might explain the increased risk of sudden overnight deaths in young type 2 diabetic patients. QT dispersion is difficult to measure consistently with interobserver variability in QT-dispersion measurements rising as high as 30%, particularly if ECG morphology is abnormal. There is a clear relation between QT measurement error and ST-T amplitude and during hypoglycaemia, ECG morphology alters, with flattening of the ST segment. Thus, although we believe this observation may be worthy of further investigation. The findings of this study suggest that 90 days administration of Vildagliptin and insulin had increased effect on heart rate, showed some trends of reduced BP and elevation in cardiac enzyme elevation in humans[20].

Activation of the sympathetic system has numerous implications, including surges of heart rate, blood pressure but also proinflammatory and procoagulant effects and increased marker enzyme levels in serum figure-3. This partially explains the increased cardiovascular adverse events noted with these DPP4i group of drugs[21].
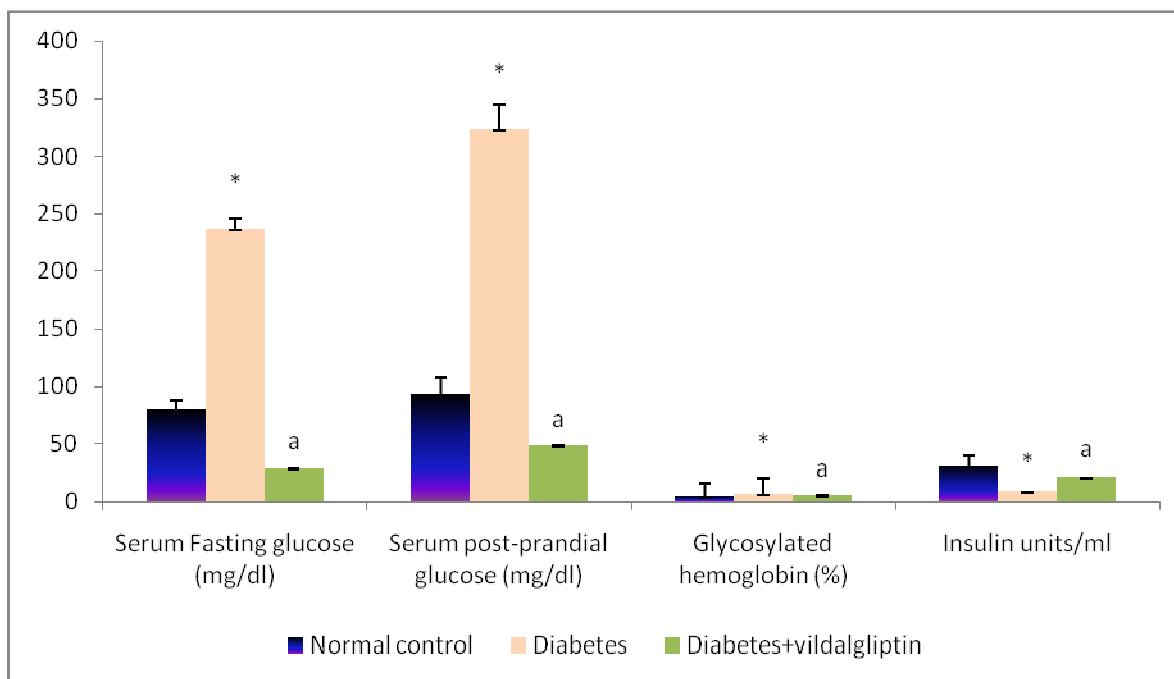

Figure-1
Effect of insulin + vildalgliptin treatment on blood glucose level, HbA1C and Insulin levels in patients in taking the dose for 90 days. Results are expressed as mean ± S.E.M, n = 10. *P < 0.001, statistically significant as compared with control rats and ^aP < 0.001 statistically significant as compared with diabetic patient group
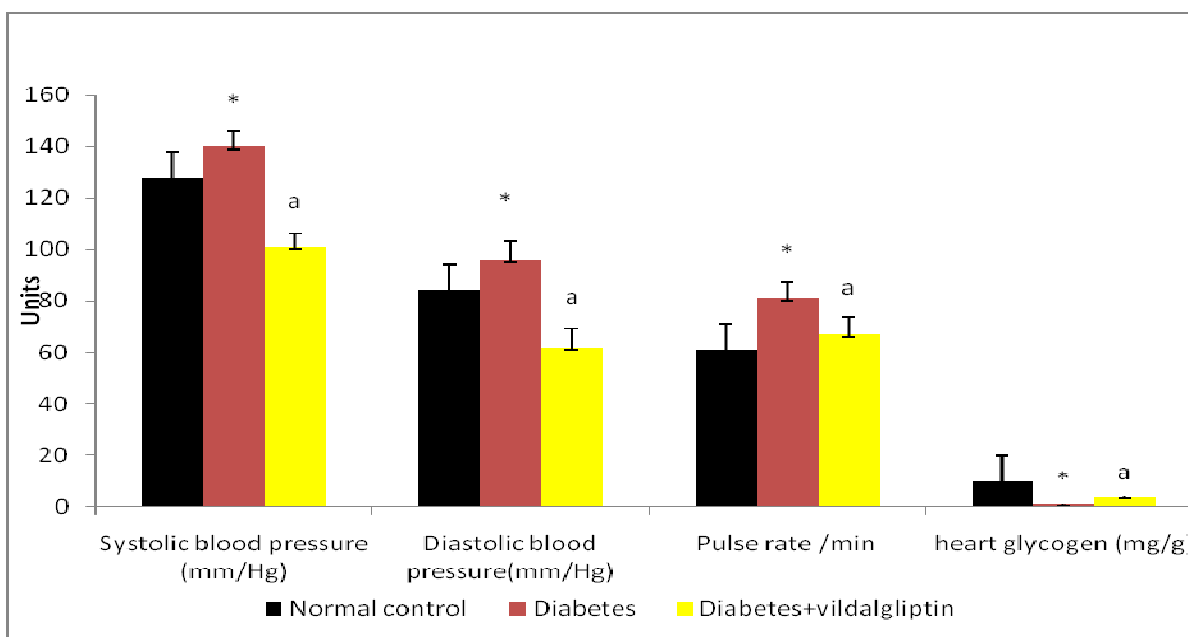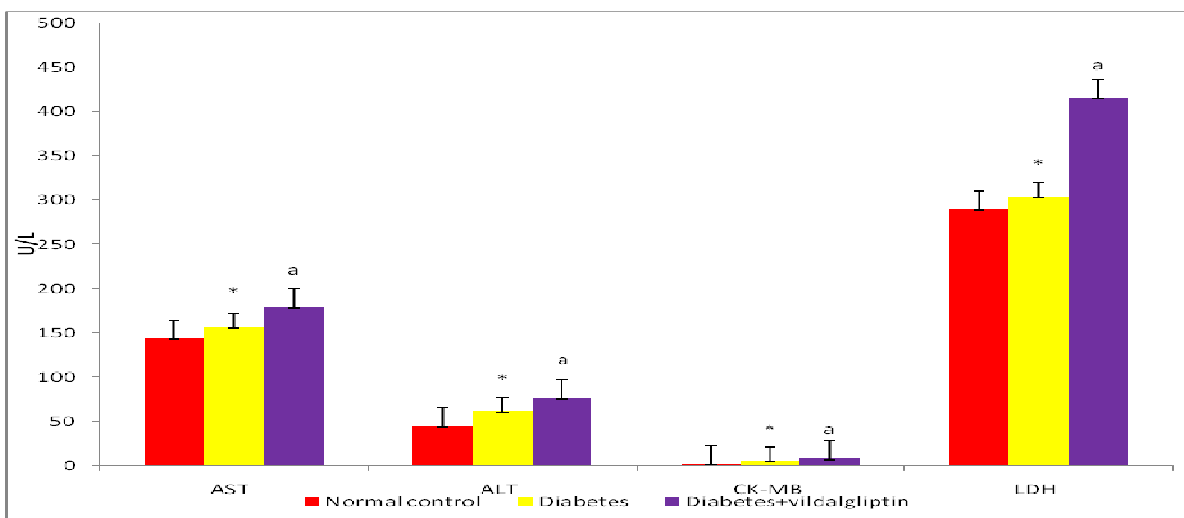

Figure-2
Effect of insulin + vildalgliptin treatment on blood pressure, pulse rate and heart glycogen levels in patients in taking the dose for 90 days. Results are expressed as mean ± S.E.M, n = 10. *P < 0.001, statistically significant as compared with control rats and ^aP < 0.001 statistically significant as compared with diabetic patient group
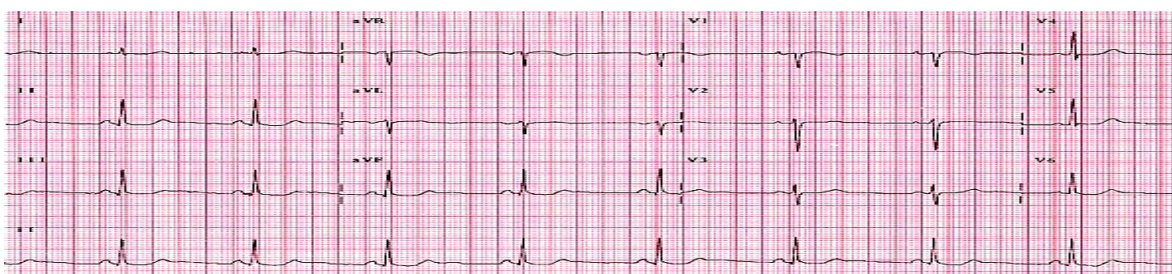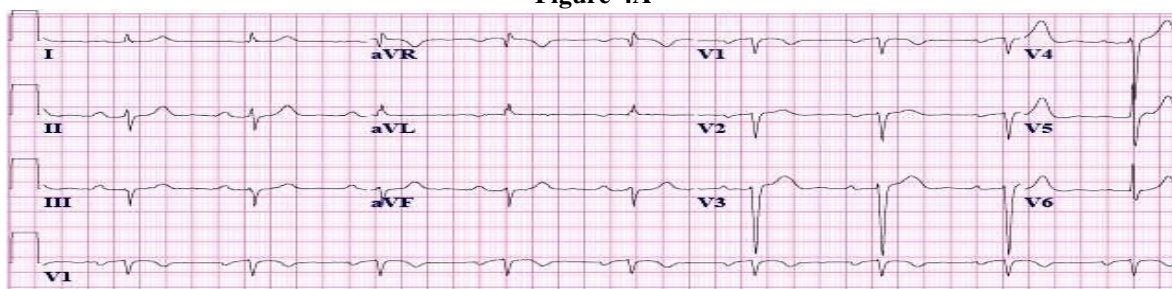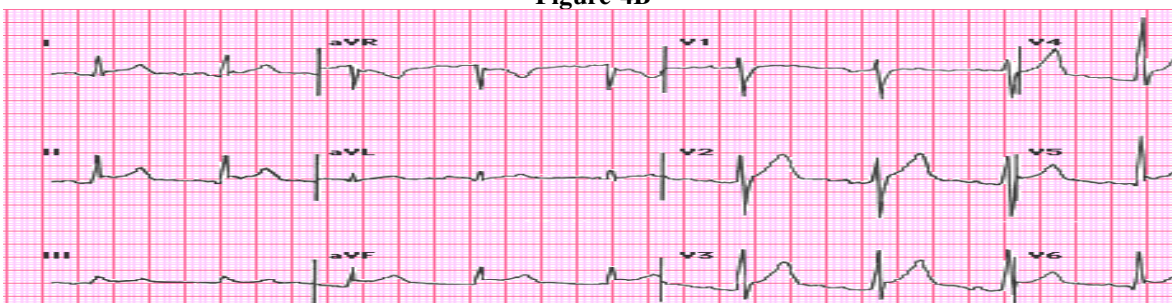
Figure-3
Effect of insulin + vildalgliptin treatment on cardiac marker enzyme levels in patients in taking the dose for 90 days. Results are expressed as mean ± S.E.M, n = 10. *P < 0.001, statistically significant as compared with control rats and [a]P < 0.001 statistically significant as compared with diabetic patient group

Figure-4A

Figure-4B

Figure-4C
This Electrocardiogram depicts the PQRST wave alteration after the treatment with combined therapy of insulin + vildalgliptin for the period of 90 days. Figure 4A – ECG signals of normal group, Figure 4B – ECG signals of Diabetes patient and Figure 4C- ECG signals of insulin + vildalgliptin treated group

Conclusion

The patients who are taking the combined therapy of insulin and vildalgliptin are more prone to cardiovascular dysfunction. Larger subsequent studies should clarify the effect of Vildagliptin on trends in other organ markers to explore the potential of overall risk of using this drug for diabetes type II patient.

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