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Adverse Drug Reactions of Combinatorial Therapy of Vildagliptin and Insulin

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A B S T R A C T

The progressive nature of the type-2 diabetes makes it necessary for the diabetic patients to take insulin as add on therapy to oral antidiabetic agents in order to maintain adequate diabetic control. But the insulin therapy is very effective in controlling the hyperglycemia during fasting but it is not effectively reducing hyperglycemia postprandially. So these drawbacks can be overcome by taking or combining insulin with other oral antidiabetic agents like incretin based therapies like vildagliptin and it enhances glucagon counter regulation and also it increases the glucose sensitivity of both alpha and beta cells. The effectiveness of combining vildagliptin with insulin has been shown by decreasing A1C levels causing hypoglycaemia. But the adverse effects of vildagliptin and insulin can be seen in their effects on different biochemical parameters and histopathological changes in the pancreatic and brain tissues.

Keywords: Insulin, Vildalgliptin, hypoglycaemia, adverse effects

A R T I C L E I N F O

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1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia Type 2 (T2DM) previously referred to as noninsulin-dependent diabetes mellitus (NIDDM) is the most common type of diabetes and is characterized by varying severities of insulin resistance [1, 2]. While the current T2DM drugs that enhance insulin release have been

therapeutically beneficial, they are associated with several side effects including unpredictable hypoglycaemia. A new class of bioactive agents called incretins, originally developed to counter postprandial hyperglycaemia, has been observed to be capable of enhancing beta cell survival, thus contributing to the long-term, optimal regulation of insulin secretion.

The development of drugs that regulate pancreatic beta cell mass will be a strong tool in the management of patients with T2DM [4]. Among them vildagliptin plays a major role in the regulation of type-2 diabetes mellitus. Vildagliptin (LAF237) marketed as Galvus® is the second DPP-4 inhibitor to be approved, in 2008, in the Europe Union for the management of diabetes mellitus. Vildagliptin has a high affinity for DPP-4 [5, 6, 7].

This strong affinity enables vildagliptin to induce large reductions in the plasma HbA1c level of patients with T2DM [8]. In addition, vildagliptin increases fasting and postprandial GLP-1 level, and induces pancreatic beta cell sensitivity to glucose and insulin. It also has the ability to significantly lower postprandial lipaemia. In contrast to many other DPP-4 inhibitors, vildagliptin does not slow the outward flow of food from the stomach to improve glucose tolerance and achieve normoglycemia [9-11]. Apart from all the above effects vildagliptin will produce the following adverse effects i.e the GLP-1 produced by vildagliptin increased cardiac output, and reduced LV end diastolic pressure, in association with improved myocardial insulin sensitivity and myocardial glucose uptake in rats with rapid pacing induced congestive heart failure [10].

Consistent with the cytoprotective action of GLP-1long-term treatment with the DPP-4 inhibitor vildagliptin, started immediate or late after MI, does not preserve cardiac function in a rat post-MI remodelling model of chronic heart failure despite increases in plasma active GLP-1 levels by inhibiting DPP-4 activity [4]. Other study showed that vildagliptin can significantly increase insulin release [12] with a simultaneous reduction in glucagon levels especially in the postmeal period [13, 14]. Insulin dosage is a real challenge in a renally impaired population due to impaired Vascular Health and Risk Management catabolism and clearance of insulin [15]. The renal clearance of insulin shows little change if the glomerular filtration rate (GFR) is above 40 mL/min, but it falls precipitously with further progression of chronic kidney disease, especially when GFR is less than 15–20 mL/min.

2. Materials and Methods

Animals and Drug Infusion:

Male Wistar rats weighing 150-200gms were used. Diabetes was induced by using freshly prepared solution of alloxan monohydrate dissolved in normal saline to 18 hr fasted rats as a single dose (150 mg/kg; intra peritoneally). Rats were divided into five groups consist of 6 animals in each group. Group-I normal control rats received saline (1ml/kg b.wt),Group II diabetes induced by alloxan of 150mg/kg as a single dose will be administered i.p, Group III diabetic animals treated with vildagliptin (0.69mg/kg b.wt) given orally as a single dose for 10 days (Burkey et al., 2005).

In Group IV diabetic animals treated with insulin of (0.27 I.U/kg b.wt) will be administered i.m as a single dose for 10 days (Rodríguez et al., 2012). Diabetic animals treated with insulin (0.27 I.U/kg b.wt) and vildagliptin (0.69mg/kg b.wt) for 10 days.All animal protocols were approved and conducted according to the recommendations of the committee for the purpose of control and supervision on experiments on animals with an awarded IAEC No:03/006/2014

Histological Examination:

The organs that were excised from the animals under the control group were cut. Organs such as liver, kidney, brain, heart, testis and pancreas were immersed in 10% formalin solution and after tissue processing, they were embedded in paraffin wax and thin sections of 5µm thickness were cut down and stained using haematoxylin and eosin for microscopic examinations.

Oral Glucose Tolerance Test:

After rats were fasted for 18 h, glucose was orally administered (2 g/kg). Blood samples were obtained before and 30, 60, 90, and 120 min after glucose loading. Blood glucose concentrations were measured immediately with a blood glucose monitor (Accu-Check, Roche).

Body and Heart Weight:

Body weight and heart weight after 10 days of treatment are shown in Table 1.We observed no significant difference in the body weight among the five groups at the beginning of the study but in the diabetic control there is a significant weight reduction of about 15gms, after vildagliptin and insulin monotherapy there is a small increase in weight with no much difference in the weight between them whereas in the combinatorial therapy there is further a small increase in body weight. With regard to heart weight in diabetic control there is a minor decline in weight but in vildagliptin and insulin monotherapies there is a mild improvement in the weight of the heart whereas in combinatorial therapy there is again a fall in the weight of the heart.

Biochemical Estimation:

The biochemical parameters like Creatinine, Uric acid, Urea, Protein and Glucose were measured by spectro-photometric methods.

3. Results and Discussion

Histology:

In this study we have done the histopathological study of pancreas & brain tissues collected from wistar rats and interpreted the damage caused by the drug vildagliptin as well as in combinatorial therapy with alloxan and insulin. Pancreatic tissue of control rats showed all the characteristic features of normal tissue and normal β cells (Figure 1A).Sections from the animals treated with Alloxan are showing pancreatic tissue lesions and severe injury in the β-Cells (Fig.1B).Sections from the animals treated with alloxan and insulin are showing ameliorative action of insulin and recovery of normal β- cells.

Sections from the animals treated with alloxan and vildalgliptin are showing less inflammation in tissues compared with diabetic group (Fig. 1D).Sections from the animals treated with and alloxan and vildalgliptin +insulin shows pathological changes which include damages to β-cells, more inflammation can be seen (Fig. 1E). Brain tissue of control rats showed all the characteristic features of normal tissue (Figure 2A).

Sections from the animals treated with Alloxan are showing brain tissue lesions and neutrophil infiltration (Fig.2B).Sections from the animals treated with alloxan and insulin are showing reduced size of neutrophil infiltration and recovery of normal brain cells (Fig. 2C).Sections from the animals treated with alloxan and vildalgliptin are showing less inflammation in tissues compared with diabetic group (Fig. 2D).Sections from the animals treated with and alloxan and vildalgliptin + insulin shows pathological changes which include damages to brain cells, more inflammation can be seen (Fig. 2E).

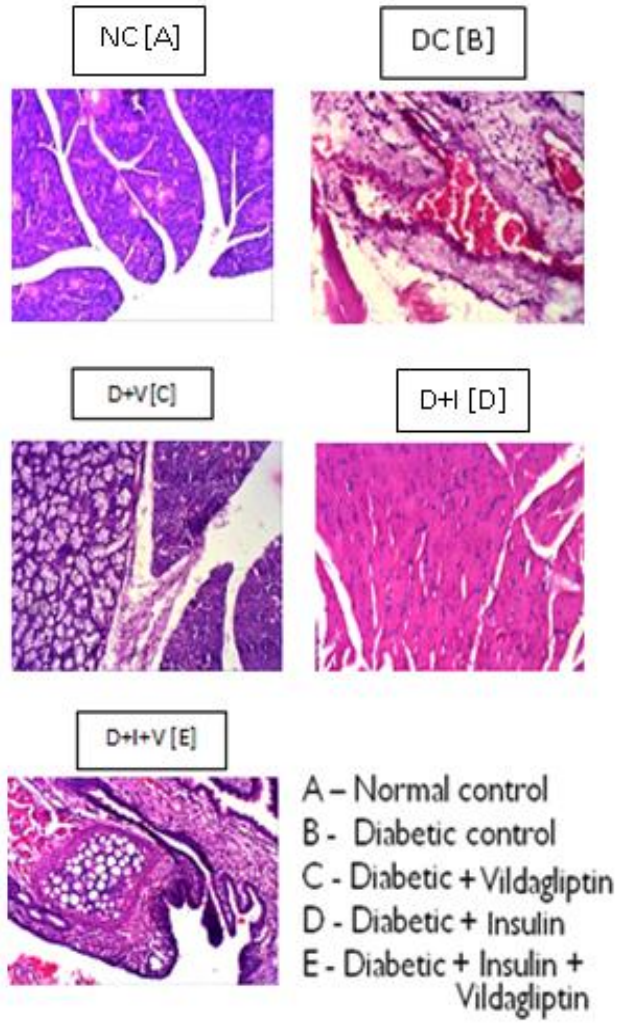

Figure 1: Effect of vildagliptin on pancreatic beta cells in alloxan-treated rats showing lesions in diabetic control and the ameliorative effect of insulin and vildagliptin as monotherapy, pathological lesions appear in combinatorial therapy.

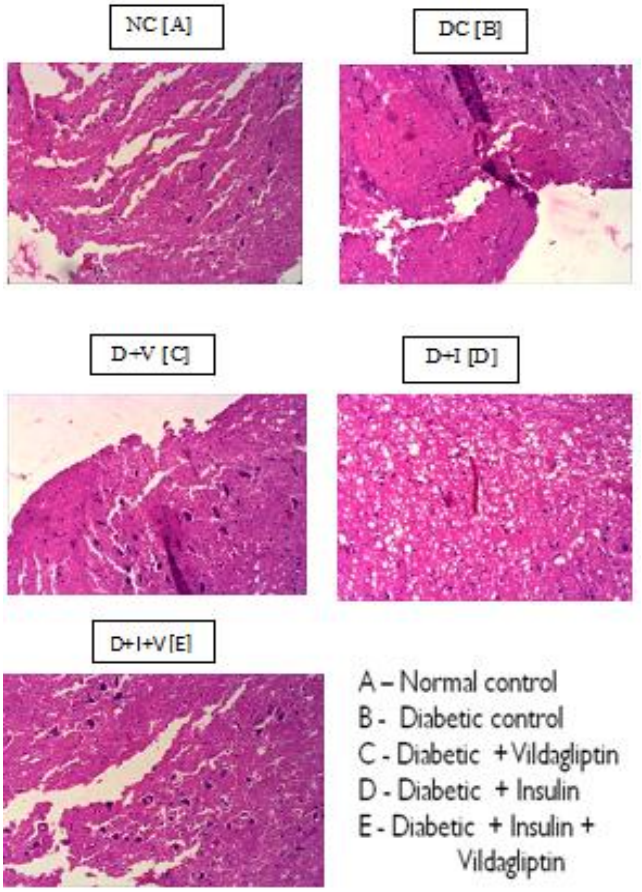

Figure 2: Effect of vildagliptin on brain cells in alloxan-treated rats showing lesions and inflammations in diabetic control and the ameliorative effect of

The Oral Glucose Tolerance Test:

The glucose tolerance test (Table.2) has been studied in the different combinations with vildagliptin as monotherapy as well as in combinatorial therapy and also in normal samples. The glucose tolerance test in different samples in different time intervals from 0 minute to 120 minutes with 30 minutes time interval has been carried out and it has shown that in normal samples there is no much difference between 0 minutes and 120 minutes of the GTT. In diabetic control and diabetic insulin also remaining the same. In vildagliptin mono as well as combinatorial therapy the difference is more i.e the glucose tolerance level is much reduced between 0 minute to 120 minutes. This shows that vildagliptin causes hypoglycaemia. This shows the decline in renal efficiency when treated with hypoglycaemic drugs. The decline in renal efficiency is more with insulin and vildagliptin combinatorial therapy when compared to monotherapy.

Biochemical Parameters: With regard to biochemical parameters like creatinine, urea, uric acid, glucose and protein (Table.3) there are a lot of variations in their levels in the monotherapy as well as combinatorial therapy of vildagliptin due to the adverse effects of the drug. With regard to the creatinine levels in diabetic control it is slightly elevated and during vildagliptin and insulin therapy it is reduced and in combinatorial therapy also it is further

reduced it shows that it is not efficiently reabsorbed in the combinatorial therapy due to decline in renal function when compared to monotherapy. With regard to the urea levels in diabetic control it is slightly elevated and during vildagliptin and insulin therapy it is reduced and in combinatorial therapy also it is further reduced it shows that it is not efficiently reabsorbed in the combinatorial therapy due to decline in renal function. With regard to the uric acid levels also in the monotherapies with insulin and vildagliptin it is reduced and in combinatorial therapies there is a little reduction when compared to the normal showing that it is not efficiently metabolised in the monotherapy as well as combinatorial therapy of insulin and vildagliptin because of decline in kidney function due to the adversity of the drug. With regard to the glucose levels in diabetic control it is very high and in monotherapies it is further reduced whereas in combinatorial therapy it is further more reduced producing severe hypoglycaemia showing the adversity of the drug. Similarly with regard to the protein levels it has been very much reduced in the diabetic control and in the vildagliptin and insulin monotherapies there is a slight improvement in the protein levels whereas in the combinatorial therapy it has been very much reduced when compared to monotherapies showing that protein metabolism is very much affected in combinatorial therapy due to the failure of renal efficiency to reabsorb protein efficiently.

Discussion

GLP-1R deficient mice exhibit increased left ventricular (LV) thickness, impaired LV contractility and LV diastolic function compared with control mice [16].GLP-1 increased cardiac output, and reduced LV end diastolic pressure, in association with decreased myocardial insulin sensitivity and myocardial glucose uptake in rats with rapid pacing induced congestive heart failure [17].Consistent with the cytoprotective action of GLP-1 in the endocrine pancreas, GLP-1 increased infarct size in the isolated perfused rat heart and in animal models of myocardial ischemia [18-20]. Vildagliptin also has no effect on QTcI but an increased incidence of first-degree AV block has been reported, although an association between vildagliptin and first-degree AV block has yet to be confirmed or excluded [21]. Although there is some scientific discussion on the clinical interpretation of QT shortening, its impact on clinical outcomes is generally deemed low and intensive investigations of QTc-shortening drugs do not currently seem to be warranted for drug approval [22]. Limitations of the above study relative to the present clinical practice of insulin therapy include the high mean daily dose of insulin that suppresses endogenous insulin secretion, the significant use of short-acting insulin, as well as the absence of metformin, ie, the exclusive use of insulin monotherapy. A further study evaluating vildagliptin in combination with insulin, intended to be more reflective of the current clinical use of insulin therapy, was therefore performed in 2011[23]. This was a 24-week, multicenter, randomized, double-blind study comparing the effects of vildagliptin (50 mg bid, n = 228) with placebo (n = 221) added to ongoing insulin therapy, with or without metformin [24, 25]. Despite the mean A1C after 24 weeks of treatment with vildagliptin being below 7%, where hypoglycemia becomes increasingly more frequent with conventional intensification of treatment, the two treatment groups had an overall comparable hypoglycemia profile.

Table 1: Study of Body Weight & Heart Weight in Insulin and Vildalgliptin Treated Rats

Group	Initial weight (gm)	Final body weight (gm)	Heart weight (gm)
Control	180 ± 1.1	200 ± 2.0	0.96 ± 0.39
Diabetic control	180 ± 1.5*	165 ± 1.5*	0.85 ± 0.53*
Diabetic + vildalgliptin	180±1.9	175±1.4	0.92 ±0.69
Diabetic + insulin	180 ± 1.6[a]	170 ± 1.2 [a]	0.93 ± 0.30
Diabetic + insulin + vildalgliptin	180±1.1 [a]	185 ±1.9 [a]	0.81 ±0.41 [a]

Results are expressed as mean ± S.E.M, n = 6. *P < 0.001, statistically significant as compared with control rats and [a]P < 0.001, statistically significant as compared with diabetes + insulin + vildagliptin treated animals.

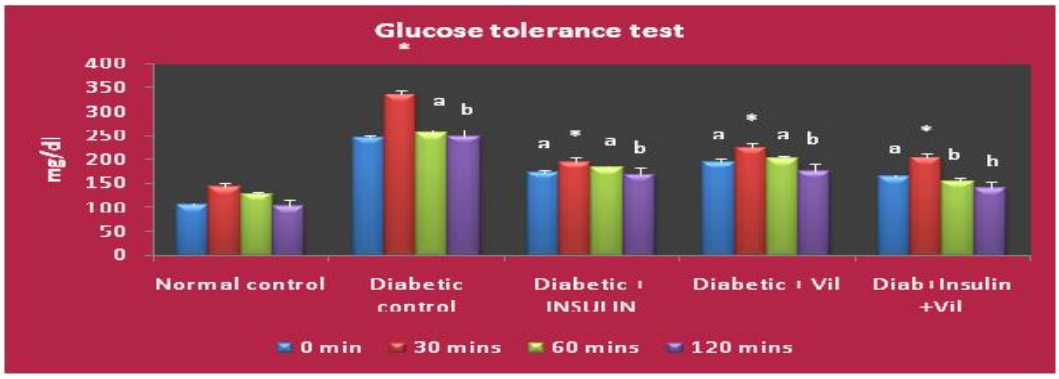

Figure 3: Depicting the Glucose tolerance test conducted on various groups

*P<0.001, statistically significant as compared with control rats: [a]P < 0.001, statistically significant as compared with diabetic rats and [b]P<0.001, statistically significant as compared with normal.

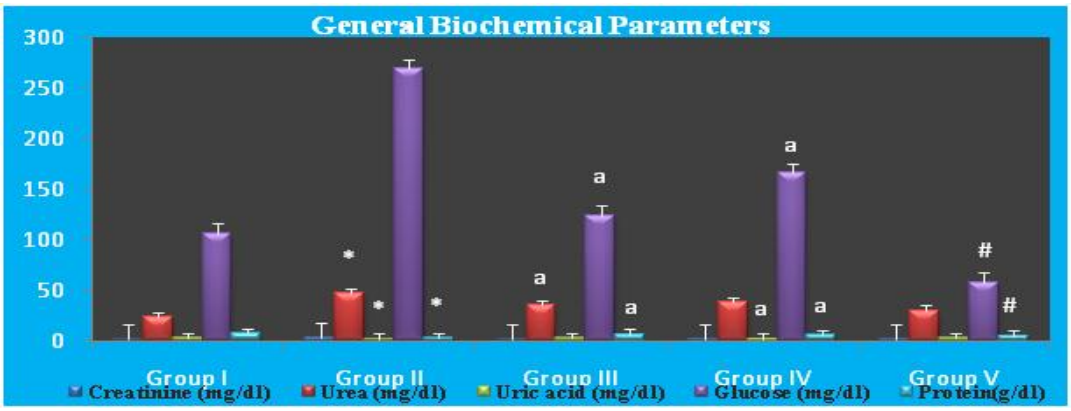

Figure 4: Depicting the General biochemical parameters conducted on various groups

*P<0.001, statistically significant as compared with control rats: [a]P < 0.001; [b]P < 0.01 , statistically significant as compared with diabetic rats and #P<0.001, statistically significant as compared with normal.

4. Conclusion

With the above tests and findings on various biochemical parameters and histopathological parameters it has been clearly proved that vildagliptin in monotherapy as well as in combinatorial therapy with insulin and alloxan produces severe renal damage as well as hepatocellular damage as well as damage of various tissues of brain and heart and liver. So in the future we are going to make these studies in human also as the use of vildagliptin & insulin in mono as well as combinatorial therapy produces severe adverse effects on the body tissues so as to enable for its usage to be banned atleast in the future to protect the future generations from its adversity.

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