ORIGINAL ARTICLE

Efficacy and Tolerability of Dianex in Type 2 Diabetes Mellitus: A Non Randomized, Open Label Non-Comparative Study

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Summary

Objective and study design: A nonrandomized open labeled clinical trial to evaluate the efficacy and tolerability of Dianex (a poly herbal formulation developed by Apex Laboratories [PVT] Chennai, Tamil Nadu, India) in type 2 diabetes mellitus was carried out during a 6-month period. Settings/location: This study was conducted in TMA Pai Hospital, Udupi, South India. Subjects: A total of 40 patients were recruited for this study. Three patients dropped out of the study leaving a total of 37 patients (11 for monotherapy and 26 for add on therapy). Outcome measures: Eighteen (18) clinical variables were investigated, including liver enzymes, kidney function tests, hematologic parameters, blood glucose, and insulin and lipid profiles. Results: at the end of 12 weeks it was found that there was a significant decrease in the level of glycated hemoglobin, fasting plasma insulin level, insulin resistance, and systolic and diastolic blood pressure. At the end of 24 weeks results were similar to those at 12 weeks. Dianex did not alter the liver function tests, hematological parameters, or kidney function tests. Conclusion: In this preliminary study, Dainex is found to be an effective adjuvant drug with either oral antidiabetic agents or insulin that can be used in the control of blood sugars in diabetic patients. Dianex is a safe drug that does not cause any clinical, hematological or biochemical alteration in major organ systems.

Key Words: Dianex, Non randomized, Open label, Type 2 diabetes mellitus

Introduction

Diabetes mellitus is state of chronic hyperglycemia, classically associated with symptoms of excessive thirst and hunger, and increased urine volume. The global prevalence of diabetes is predicted to rise from 135 million in 1995 to 300 million by 2025[1]. Today, India has 25 million diabetic patients, more than any other country, and the number is expected to rise to 35 million by 2010 and to 57 million by 2025[2]. Diabetes is ranked among the top five killers in most countries because of the associated risks such as stroke, ischemic heart diseases and renal failure. Worldwide, considerable advances have been made in the management of diabetes and its complications in recent years. Despite improved understanding of its pathogenesis and the identification of the various risk factors, prevention of the disease and/ or its complications still pose formidable problems.

The present treatment options for treating type 2 DM are oral anti-diabetic agents and insulin. There are a

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variety of oral agents available, which work through either insulin secretogogue effect or by decreasing insulin resistance. These agents have remained the mainstay of oral hypoglycemic treatment for more than 30 years. However, maintaining glucose control in these patients remains a difficult task[3].

In India, Ayurvedic medicine is reported to have been successfully used[4]. As an alternative mode of treatment, Ayurvedic medicine has been claimed to be less toxic and more efficacious. Dianex is a poly herbal formulation developed by Apex Laboratories Chennai, each tablet of which contains *Gymnema sylvestre, Eugenia jambolana, Mormodia charantis, Withania somnifera, Cassia auriculata, Curcuma longa, Aegle maremlos and Azadiratchta indica*. Dianex, in preclinical studies done at the College of Pharmaceutical Sciences in Manipal was found to be effective in lowering the blood sugar level in diabetic rats[5]. In addition it was found to reduce serum lipid profiles and blood pressure. This could be a welcome bonus for patients who often have to take many drugs to control the additional clinical problems. Further no acute or chronic toxicity was noted in rats during these studies.

Having thus confirmed the safety of the preparation, the present study was undertaken to determine the effects of Dianex on blood glucose, lipid profile and blood pressure in type 2 DM patients along with monitoring of its safety profile in humans.

Materials and Methods

This was an open labeled non-randomized non-comparative study to determine the efficacy and safety of Dianex. The study was carried out after obtaining clearance from the Institutional Ethics Committee. Forty type 2 DM patients were enrolled for the study after taking informed consent. At the time when Dianex was started, they had uncontrolled blood sugar levels. All patients were instructed to report any adverse events to the investigators immediately. Table I shows the general characteristics of the 37 subjects.

Patients included in the monotherapy group were either newly diagnosed diabetics not on any drugs or patients with mild diabetes controlled with small doses of oral anti-diabetic agents. The second category of these patients were given a wash-out period of a week in order to avoid interference from other drugs and then started on Dianex after recording baseline values.

Patients whose diabetes was uncontrolled with oral anti-diabetic agents and/or insulin were given Dianex in addition and were included in the add-on group. The dose of the OHAs/insulin was not increased throughout the study. Dianex was started at the dose of 1 tablet thrice daily and increased gradually depending on the sugar values to 2 tablets thrice daily.

Detailed history and thorough physical examination including height, weight and BMI were done in all the patients. All patients underwent baseline investigations including blood sugars, fasting insulin, lipid profile and other safety parameters such as urea, creatinine, and liver enzymes. Based on the values of fasting insulin and plasma insulin, insulin resistance was calculated using the HOMA model in all patients at baseline and 12 weeks.

Dianex was started after the baseline investigations and titrated based on fortnightly fasting and post-prandial blood sugar estimations. All the clinical variables including pulse, blood pressure, and systemic examination were recorded at each visit. At each visit, patients were asked to report if they had any untoward side effects. At the end of 12 weeks, physical examination, baseline biochemical and hematological investigations for documenting efficacy and safety were repeated. All these parameters were recorded in a separate study case record form in addition to the patients' case sheet.

The first five patients included in the study were hospitalized. Among these, there were 2 patients in the monotherapy group and 3 patients in the add-on group. Fasting blood sugar (FBS) and PPBS were done daily in these patients in order to arrive at the dose of Dianex that should be recommended to all patients.

Inclusion criteria: Only patients fulfilling all the following criteria were included: Age >35 years; both males and females and type 2 diabetes mellitus controlled or uncontrolled with oral antidiabetic agents. **Exclusion criteria:** Patients were excluded for the following reasons: Patients with type 1 diabetes mellitus; patients with hepatic dysfunction; kidney dysfunction; presence of debilitating illness; significant neurologic or psychiatric illness; patients with glaucoma; pregnant women; and patient who have taken any other investigational drug within the preceding month.

Statistical analysis was done using paired't' test using the SPSS statistical software.

Results

Forty patients were enrolled to the study, but three were lost to follow-up. Hence, the results of 37 patients (11 in monotherapy and 26 in add-on groups) were analyzed. Analysis was done at two stages, 12 weeks and 24 weeks.

Analysis at 12 Weeks

Analysis of all patients (Table II):

There was a very significant reduction of mean glycosylated hemoglobin from 11.1% to 9.9% (p=0.001). However, there was no significant reduction of either fasting or post-prandial glucose levels. There was a significant reduction of fasting plasma insulin level, insulin resistance, and systolic and diastolic blood pressures. Fasting plasma insulin level reduced from 49.8 μU/L to 36.2 μU/L, Insulin resistance reduced from 18.5 to 12.3 and beta cell function came down from 244.4 to 221.7. All these reductions were statistically significant. However, it was noted that serum lipid levels were adversely affected with an elevation of total cholesterol and triglycerides with reduction of HDL cholesterol, though not all these were statistically significant.

Safety parameters at 12 weeks:

All the patients tolerated Dianex well and no clinical adverse effects were noted in the course of the study. There were no significant adverse effects on hematological, renal and liver function parameters (Table III).

B. Results of monotherapy sub-group (Table IV):

In this group, though there was some improvement in glycosylated hemoglobin, fasting insulin, insulin resistance, total cholesterol and HDL cholesterol levels, they were not statistically significant and there was no reduction in fasting or post-prandial glucose levels. Glycosylated hemoglobin reduced from 10.1% to 10.0%, fasting insulin came down from 38.9 mU/L to 35.1 mU/L, insulin resistance decreased from 14.2 to 12.2 and beta cell function came down from 182.1 to 161.7. There was some reduction in total cholesterol from 215.7 mg% to 209.5 mg%, LDL-cholesterol from 129.9 mg% to 128.1 mg% and triglycerides from 141.9 mg% to 127.8 mg%. However, HDL-cholesterol reduced from 57.3 mg% to 56.8 mg%. These changes were not statistically significant. There was a reduction in systolic and diastolic blood pressures, but only reduction in diastolic BP reduction was statistically significant. Diastolic blood pressure came down significantly from 80 mmHg to 74 mmHg while systolic blood pressure reduced from 127 mmHg to 121 mmHg.

Results of the add-on sub-group (Table V):

In this group, there was a very significant reduction of glycosylated hemoglobin levels. Glycosylated hemoglobin level reduced from 11.6% to 9.8% (p=0.001). However, there was no statistically significant reduction of either fasting or post-prandial glucose levels. Fasting insulin, insulin resistance, and systolic and diastolic blood pressures showed a statistically significant reduction. Fasting plasma insulin level reduced from 54.5 μU/L to 36.6 μU/L, Insulin resistance reduced from 20.3 to 12.3 and beta cell function came down from 270.7 to 247.0. All these reductions were statistically significant.

However, there was significant elevation of total cholesterol, triglycerides, and LDL cholesterol and a significant reduction of HDL-cholesterol. Total cholesterol increased from 192.7 mg% to 202.7 mg%, LDL-cholesterol from 112.6 mg% to 123.3 mg%. Serum triglyceride levels increased from 153.9 mg% to 173.1 mg% and HDL-cholesterol level came down from 48.4 mg% to 45.4 mg%.

Results at 24 Weeks:

Thirty patients completed 24 weeks of Dianex therapy. Dianex therapy was discontinued in seven patients in view of inadequate blood sugar control. All the patients in the monotherapy group required the addition of an oral hypoglycemic agent as they remained uncontrolled and hence were not analyzed. The results of the add-on group are presented here.

Results of the add-on sub-group (Table VI):

At 24 weeks, the results were similar to that at 12 weeks. Fasting blood sugar reduced to 143.6 mg% from 147.6 mg%. PPBS came down from 227.7 mg% to 217.8 mg%. These changes were not statistically significant. However, the change in glycosylated hemoglobin was very significant (p<0.001). It reduced from 11.6% at baseline to 9.8 % at 12 weeks and to 9.1 % at 24 weeks. There was a smooth reduction in systolic and diastolic blood pressure also which was statistically significant.

Table I: General characteristics of the study group:

Characteristics	Mean ± SD
Age in years	57.1 ± 12.6
Sex ratio (M:F)	17:20
BMI	23.7 ± 5.1
WHR	0.97 ± 0.07

BMI, body mass index,
WHR, waist hip ratio.

Table II: Mean value of laboratory tests before and after treatment (n=37)

Parameters	Mean ± SD (0 wk)	Mean ± SD (12 wk)
FBS (mg/dL)	147.6 ± 38.3	146.9 ± 54.8
PPBS(mg/dL)	220.4 ± 76.0	215.2 ± 73.3
HbA1c*(%)	11.1 ± 2.3	9.9 ± 1.6
Fasting Insulin**(µg/L	49.8 ± 47.7	36.2 ± 21.3
Insulin Resistance**	18.5 ± 22.0	12.3 ± 10.2
Beta Cell Function	244.4 ± 195.7	221.7 ± 169.2
Total cholesterol (mg %)	199.2 ± 43.2	208.5 ± 48.3
Triglycerides (mg %)	150.5 ± 70.0	165.1 ± 125.4
LDL - C(mg %)**	117.6 ± 31.3	124.1 ± 35.4
HDL- C(mg %)	50.9 ± 12.2	48.2 ± 11.1
Systolic BP (mm Hg)	134.1 ± 18.4	126.5 ± 14.8
Diastolic BP (mm Hg)	81.6 ± 7.7	77.1 ± 7.1

*P< 0.001, **P<0.05 pre and post treatment groups

Table III: Hematological, renal and liver function parameters before and after treatment

Parameter	Mean ± SD (0 wk)	Mean ± SD (12 wk)
Hemoglobin (g %)	11.8 ± 1.5	13.6 ± 1.0
Total WBC count(cells /cu ml)	9400 ± 1617	8170 ± 3085
ESR(1st hr)	28.0 ± 19.3	38.2 ± 30.9
B. urea (mg%)	22.3 ± 5.7	19.2 ± 5.3
S. creatinine(mg%)	0.9 ± 0.15	0.83 ± 0.09
AST(IU/L)	28.1 ± 14.9	32.0 ± 17.3
ALT(IU/L)	31.1 ± 17.3	32.0 ± 16.1

Table IV: Results of monotherapy group (n=11)

Parameters	Mean ± SD (0 wk)	Mean ± SD (12 wk)
FBS (mg/dL)	147.6 ± 42.3	145.8 ± 62.9
PPBS (mg/dL)	227.7 ± 82.7	213.5 ± 72.3
HbA1c** (%)	11.6 ± 2.4	9.8 ± 1.4
Fasting Insulin* (µg/L)	54.5 ± 54.9	36.6 ± 22.5
Insulin Resistance*	20.3 ± 25.6	12.3 ± 10.4
Beta Cell Function	270.7 ± 216.7	247.0 ± 192.2
Total cholesterol* (mg %)	192.7 ± 39.8	202.7 ± 50.2
Triglycerides (mg %)	153.9 ± 73.9	173.1 ± 137.4
LDL – C*(mg %)	112.6 ± 27.6	123.3 ± 34.1
HDL- C* (mg %)	48.4 ± 10.5	45.4 ± 8.6
Systolic BP* (mm of Hg)	136.8 ± 17.8	128.8 ± 16.0
Diastolic BP*(mm of Hg)	82.3 ± 7.7	78.2 ± 7.6

*P < 0.05, **P<0.001 pre and post treatment comparison

Table V: Results of the add-on group (n=26)

Parameters	Mean ± SD (0 wk)	Mean ± SD (12 wk)
FBS (mg/dL)	147.6 ± 42.3	145.8 ± 62.9
PPBS (mg/dL)	227.7 ± 82.7	213.5 ± 72.3
HbA1c** (%)	11.6 ± 2.4	9.8 ± 1.4
Fasting Insulin* (µg/L)	54.5 ± 54.9	36.6 ± 22.5
Insulin Resistance*	20.3 ± 25.6	12.3 ± 10.4
Beta Cell Function	270.7 ± 216.7	247.0 ± 192.2
Total cholesterol* (mg %)	192.7 ± 39.8	202.7 ± 50.2
Triglycerides (mg %)	153.9 ± 73.9	173.1 ± 137.4
LDL – C*(mg %)	112.6 ± 27.6	123.3 ± 34.1
HDL- C* (mg %)	48.4 ± 10.5	45.4 ± 8.6
Systolic BP* (mm of Hg)	136.8 ± 17.8	128.8 ± 16.0
Diastolic BP*(mm of Hg)	82.3 ± 7.7	78.2 ± 7.6

*P < 0.05, **P<0.001 pre and post treatment comparison

Table VI: Results of the add-on group (n=21)

Parameter	Mean ± SD(0 wk)	Mean ± SD (24 wk)
FBS (mg/dL)	147.6 ± 42.3	143.6 ± 38.9
PPBS (mg/dL)	227.7 ± 82.7	217.8 ± 44.4
HbA1c (%)*	11.6 ± 2.4	9.1 ± 1.6
Systolic BP(mm Hg)**	136.8 ± 17.8	126.0 ± 17.1
Diastolic BP(mm Hg)**	82.3 ± 7.7	77.2 ± 8.9

*P< 0.001, ** P< 0.05 pre and post treatment comparison

Discussion

In this non randomized open label non-comparative study, Dianex was found to be effective in controlling hyperglycemia as evidenced by a very significant decrease in glycosylated hemoglobin from 11.1% to 9.9% ($p<0.001$). Glycosylated hemoglobin is the specific indicator of diabetic control in any patient over the preceding 12 weeks[6]. As this trial was carried out over a 3-6 month period, the difference in glycosylated hemoglobin from baseline to 12 weeks proved the efficacy of Dianex. This significant reduction was best seen in the add-on group (from 11.6% to 9.8%, $p<0.001$). However, in the monotherapy group the reduction in glycosylated hemoglobin was not significant ($p< 0.86$). This suggests that Dianex may not be very effective as a single drug for control of blood sugars. However, in combination with other anti diabetic drugs, the drug shows very significant synergetic effect.

In both the monotherapy and the add-on groups, the fasting and post-prandial sugars were did showing much change. This could be attributed to variations in these values on a daily basis due to diet and other variables. In all major studies, glycosylated hemoglobin is taken as the gold standard for documentation of glycemic control and hence more importance should probably be given to the improvement in this parameter[7].

We tried to elucidate the mechanism by which Dianex acts by investigating the insulin related parameters and beta cell function. Fasting insulin was done at baseline and 12 weeks and the insulin resistance was calculated using the HOMA model[8]. It was found that when all patients were analyzed insulin resistance reduced significantly from 18.52 to 12.3 ($p=0.028$). Beta cell function was found to decrease, though not significantly, possibly as a consequence of reduced insulin resistance in the periphery. This suggests that Dianex reduces insulin resistance thereby improving the glycemic control and not through over stimulation of the beta cells as done by sulfonylurea[5]. Despite the fact that this results in good glycemic control in the short term, over stimulation of the beta cells can ultimately lead to beta cell exhaustion and secondary failure of this group of drugs[9]. Dianex would be an ideal adjunctive drug for such situations as it reduces beta cell function and delays the onset of beta cell failure and resultant secondary failure.

This concept is the focus of research in recent times and many drugs that reduce insulin resistance have been developed. Among these, the glitazones are the foremost and Dianex has a very similar profile of effect on insulin resistance and beta cell function. When the monotherapy group was analyzed separately, both fasting insulin and insulin resistance decreased but did not achieve statistical significance. This was probably due to the small number of patients in this study group and further studies with a larger study sample may be needed to confirm this trend. In the add-on group, the reduction in fasting insulin and insulin resistance was statistically significant as all patients in the add-on group received only Dianex as an extra tablet and no changes were made in the concomitant medication except to decrease the medicine when glycemic control was achieved. This trend could be attributed to Dianex alone. As most patients with type 2 diabetes have a major component of insulin resistance and hyperinsulinemia, this attribute of Dianex is an attractive proposition as an add-on agent that tackles the major basic pathophysiology behind type 2 diabetes mellitus.

Beta cell exhaustion is a part of the natural decline of beta cell function in type-2 diabetes. Hence reduction in the insulin resistance and consequent reduction the beta cell function may spare the beta cell from early exhaustion. This is one of the main aims of treatment of type-2 diabetes. This trend could be used to advantage in these patients.

Dianex was found to have a significant effect on blood pressure in all patients, both systolic and diastolic blood pressure were reduced from 134.1 to 126.5 and from 8.1.6 to 77.1 ($p=0.009$ and 0.004) respectively in all patients. When this result was analyzed freely for the monotherapy group the reduction in the systolic blood pressure was not significant statistically but diastolic blood pressure showed significant decrease ($p= 0.026$). In the add-on group, both systolic and diastolic blood pressure reduction was in the significant range with p value of 0.15 to 0.042.

Effect of Dianex on lipid profile and the results of lipid profile analysis of all patients in Dianex was studied. It was found that there was an insignificant increase in the total cholesterol and triglycerides. There was also a decrease in LDL cholesterol accompanied by an insignificant reduction in HDL cholesterol. As the drug was not shown to increase lipid in pre clinical studies, further subgroup analysis of lipid profile was carried

out. It was found that in the monotherapy group there was in fact no significant alteration in lipid for all parameters including total cholesterol, triglycerides, LDL and HDL. When the results of the add-on group were analyzed, there was no significant alteration in lipid profile. When these patients were individually looked at we found that 2 of them had stopped concomitant lipid lowering therapy during the course of the trial that was prescribed even before enrolling them for the trial. Subsequent alteration in lipid profile could be explained on this basis. Four patients had uncontrolled sugar at 12 weeks and the corresponding triglyceride increase could be due to this fact. However, in 4 other patients there was no obvious cause for the raise in triglycerides. The overall analysis did not show a significant raise in triglycerides.

The total cholesterol, LDL and HDL were significantly altered in the add-on group for which no obvious explanation could be given. Statistical analysis revealed wide variations on standard deviation across the mean underlining the fact that this was indeed a heterogeneous group of patients as far as lipid profile was concerned. Hence, we would suggest that this aspect of the action on Dianex must be studied independently in larger number of patient with strict supervision of their dietary habits.

Toxicity of Dianex: All patients were monitored for clinical, hematological and biochemical toxicity profile throughout the study. As explained in the consent form patients were asked to report if they experienced any gastrointestinal side effects or hypoglycemic symptoms. However, there was no such complaint from any patient. During every follow up a thorough physical examination was done to evaluate decrease in hemoglobin, jaundice or any evidence of renal dysfunction and none of these was noted in any patient. Hematological parameters such as hemoglobin, TC, DC, ESR showed no significant adverse trend. Biochemical parameters such as LFT and renal function were also done at the beginning and end of the study. There was no alteration in any of these parameters. During the course of the study an acceptability proforma was given to all patients to get feed back on how acceptable the drug was for their daily usage. More patients were comfortable with the color, presentation and taste of the drug. Some patients did complain about the large size of the tablet which made swallowing slightly uncomfortable. Many expressed willingness to continue the drug on a daily basis if it is available in the market as they perceived it as being as safe as a general natural tonic.

It is pertinent to stress the following limitations in the study which may have significant bearing on the applicability of the findings-the study was undertaken on a convenient sample and bias due to non randomization effect is quite possible.

In conclusion, this is a preliminary study that has shown promising results for Dianex. Since this is a non-comparative study, it requires validation with randomized placebo controlled clinical trials. We have also observed adverse effects on lipid profiles. This may be due to the heterogenous group of patients. This again needs a separate study on a large number of patients with strict dietary control.

References

1. King, H., Aubert, RE., & Herman, WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; 21: 1414-431.
2. Ramachandran A, Snehalatha C, Latha E. Vijay V and Viswanathan M; Rising prevalence of NIDDM in urban population in India. Diabetologica 1997; 40: 232-7.
3. Mustaffa BE. Diabetes mellitus in Asia: an increasing health care burden. Med Dig 1998; 16: 5-9.
4. John PC. Historical background. Textbook of Diabetes, 2nd ed., vol. I. London: Blackwell Science, 1997: 101.
5. Udupa N. Effect of Dianex on blood sugar, serum lipids and blood pressure in rats. Report submitted to Apex Laboratories [PVT] Ltd Chennai, India 2000.
6. Kay KH, Nicolas W, Robert L Sheila B, Suzy O, Ailsa W, Nicolas D. Glycated hemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition. BMJ 2001; 322: 15.
7. McCance, DR., Hanson, RL., Charles, M-A., Jacobsson, LTH., Pettitt, DJ., Bennett, PH., et al. Comparison of tests for glycated hemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ 1994; 308: 1323-32.
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologica. 1985; 28: 412–19.
9. Groop LC, Pelkonen R, Koskimies S, Bottazzo GF, Doniach D: Secondary failure to treatment with oral antidiabetic agents in non-insulin-dependent diabetes. Diabetes Care 1986; 9: 129-33.