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Original Research Article

Efficacy and safety of sitagliptin, metformin and pioglitazone fixed-dose combination therapy (100 mg/1000mg and 15 mg respectively) as a first-line treatment in obese type 2 diabetes with high insulin resistance

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Abstract:

Background*:* Metformin is the first line of treatment in patients with type 2 diabetes. Diabetes being a metabolic disorder, improvement does not occur just with metformin. The pharmacotherapy course then changes to a fixed combination of drugs that have complementary mechanisms to those of metformin.

Aim*:* To assess the efficacy and safety of anti-diabetic drugs individually and in combination. Here, sitagliptin was compared with a fixed dosage combination of metformin and sitagliptin and pioglitazone alone in diabetic patients who had HbA1c of more than 7.5% and less than 12.0%

Method*:* In total, 40 weeks of study were divided into two phases. Phase A patients were divided into two groups and given sitagliptin and pioglitazone. In the second phase, the patients with sitagliptin were given a combination of sitagliptin and metformin, and the second group of patients were up-titrated with the dose of pioglitazone

Results: At the end of phase A, HbA1c levels decreased in both groups, and similar results were obtained for blood sugar levels fasting as well as post-prandial. In phase B a decrease was obtained in both HbA1c and blood glucose levels in fasting and postprandial; this decrease was observed to be significant compared to the first phase. When the adverse drug reaction of the combination and individual drugs were compared, such incidences were lesser in the case of combination pharmacotherapy

Conclusion: The decrease in the glycemic levels was more in the case of combination therapy compared to monotherapy. However, both types of therapy were well tolerated.

Keywords: combination of sitagliptin and metformin, pioglitazone, treatment of type 2 diabetes mellitus

Introduction

Diabetes mellitus is a metabolic disorder that occurs because of a disruption in the ability of pancreatic beta cells to produce insulin. It is characterized by hyperglycemia and a rise in HbA1c levels. As it is a metabolic disorder it causes disturbance in the metabolism of glucose and lipids in the body [1]. Lifestyle modification and pharmacotherapy have been proven to improve the conditions. In the case of pharmacotherapy, the first line of treatment is metformin as a monotherapy [2]. If monotherapy is not sufficient in improving the HbA1c levels then combination therapy is recommended.

Various studies have reported that combination pharmacotherapy is useful in the treatment of diabetes mellitus type 2. A fixed-dose combination also improves patient compliance.

Sitagliptin acts by inhibiting dipeptidyl peptidase 4 which causes an increase in the secretion of glucose transporters which increases the glucose uptake from the blood. It decreases the synthesis of glucose and fats in the liver [3]. The overall effect is a decrease in the levels of blood sugar. Metformin is a biguanide drug that acts at the mitochondrial level and increases the adenosine monophosphate kinase in the skeletal muscles and the liver. AMPK increase in the skeletal muscle causes an increase in the glucose uptake from the blood. In the liver, AMPK decreases gluconeogenesis and synthesis of fats [4]. Since the mechanism of action of both drugs is complementary to each other, a fixed dose combination of both drugs can improve blood glucose levels significantly. Pioglitazone acts on the nuclear receptor peroxisome proliferator-activated receptor which induces and inhibits the expression of certain genes. These genes are involved in the metabolism of lipids and glucose. The synthesis of new glucose and fats in the liver decreases and the uptake of glucose from the blood increases.

A combination therapy of the above-stated drugs can help achieve ideal blood sugar levels [5]. This study aims to evaluate the safety and efficacy of combination drugs that is sitagliptin and metformin, to compare the safety and efficacy of the mentioned fixed-dose combination with monotherapies of sitagliptin and pioglitazone.

Method

The patients between the age group of 18 to 78 years and had HbA1c levels between 7.5% to 12% were selected for the study. The patients who had hypersensitivity to any of the drugs in the study had been on antihyperglycemic agents in the period of the last 3 months, had type 1 diabetes, and had ketoacidosis were eliminated from the study. Randomized double-blinded studies were carried out. Patients were given a placebo in the first two weeks to get a baseline of the sugar level and HbA1c levels. Following that a 40-week study was conducted the first 12 weeks were phase A and the second phase was of 28 weeks. In both phases, patients were divided into two groups. The first group was given sitagliptine 100 mg and the other group was given pioglitazone 15 mg which was titrated up to 30 mg for phase A. In phase B, the group of patients who were given sitagliptine were now given a combination of sitagliptine and metformin. The patients who were given pioglitazone 30mg in phase A now they were given 45 mg of pioglitazone. Throughout these 40 weeks, patients were closely monitored for their blood sugar levels, HbA1c levels, and occurrence of any adverse effects. After 40 weeks also patient visited the hospital 12 times for monitoring of side effects of the drug. The primary endpoint of the study was an HbA1c level of less than 7% and a blood glucose level under control. Secondary endpoints included lipid profiling and adverse drug reactions. The data obtained was statistically analysed. Good clinical practice was followed throughout the trial.

Results

In total 300 patients were screened out of which 50 were eliminated because they had one or more exclusion criteria. Out of 250, 50 patients discontinued before the completion of the trial. The average age of patients in group 1 was 51.5 and the average age of patients in group 2 was 52.5. The mean HbA1c of group 1 before the trial was 9.0% and the patients in group 2 had a baseline of 9.1%.

To evaluate the efficacy of the drug HbA1c level, post-prandial blood sugar, and fasting blood glucose were recorded at the end of phase A. However, at the end of phase B the HbA1c level, fasting blood sugar level, post-prandial blood sugar level, triglyceride level, total cholesterol, low-density lipid

level, and high-density lipid level were recorded to evaluate efficacy.

At the end of phase A, group 1 (n=115) received sitagliptin 100 mg for 12 weeks the mean reduction of HbA1c was 1% and the other group (n=135) that received pioglitazone 15 mg that was up-titrated to 30 mg towards the end of 12 weeks had a mean reduction of HbA1c as 0.9%. The average reduction in the post-prandial sugar levels for group 1 was 53.8 mg/d/L and for group 2 it was 51.8mg/dL. The average reduction in the fasting blood sugar levels in group 1 was 27.6mg/dL and in group 2 it was 29.0mg/dL.

At the end of phase B, group 1 which received sitagliptin and metformin combination had an average reduction of HbA1c of 1.7% and group 2 which received pioglitazone 45 mg had a reduction of 1.4%. The total number of patients who had an HbA1c level lesser than 7.0% was more in group 1 compared to group 2. The average reduction in the post-prandial sugar levels for group 1 was 91.3mg/dL and for group 2 was 70.1mg/dL. The average reduction in the fasting blood sugar levels for group 1 was 46.68mg/dL and for group 2 was 38.6mg/dL.

The average total cholesterol in group 1 decreased by 0.5mg/dL and in group 2 it increased by 6.2mg/dL. The average total glycerides decreased in group 1 by 5.0mg/dL and in group 2 it decreased by 6.2mg/dL. High-density cholesterol in group 1 increased by 7.8mg/dL and in group 2 it increased by 10.6mg/dL. The decrease in the low-density lipids was observed in group 1 which was 2.5mg/dL and for group 2 the increase was 12.0mg/dL. In the case of lipid profiling the difference in both the groups for all the parameters except for low-density lipid was not statistically significant. Table no.1 summarizes all the data for efficacy of the drugs during the trial.

Table No. 1 Summary of the parameters monitored throughout the clinical trial

Parameters	Average Value	Group 1 No. of patients	Average value	Group 2 No. of patients
Phase A- 12 weeks	Sitagliptine 100 mg (n=115)		Pioglitazone 15-30mg (n=135)	
HbA_{1c}	-1.0%	109	-0.9%	130
Post prandial blood sugar level	-53.8	94	-51.8	113
Fasting blood sugar level	27.6	110	-29.0	132
Phase B- 28 weeks	Sitagliptine+ Metformin (n=100)		Pioglitazone 45 mg (n=100)	
HbA_{1c}	-1.7%	96	-1.4%	98
Post prandial blood sugar level	-91.3	73	-70.1	76
Fasting blood sugar level	-46.8	96	-38.6	99
Total cholestrol	-0.5	87	+6.2	92
Triglyceride	-5.0	87	-6.2	92
High density lipid	+7.8	86	+10.6	92
Low density lipid	-2.5	86	+12.0	92

The drugs were well tolerated in both the groups and the adverse drug reactions were comparatively more in the case of the group that received pioglitazone. However, the difference in the occurrence of the adverse drug reaction was not significant statistically. Adverse drug reactions included nausea, hypoglycemia, abdominal pain and diarrhoea with all three drugs. Also in the group that received pioglitazone adverse drug reaction, oedema. None of the adverse drug reactions required management or treatment they resolved within a day or two.

Discussion

In phase A of the trial, there was a significant decrease in the HbA1c levels, fasting blood sugar levels, and postprandial sugar levels in both groups. Considering group 1 which received sitagliptine the difference in the levels from the baseline was substantial, although it was dependent on the baseline values as well. If the baseline was high, then the decrease in the levels was more substantial. On the contrary, this was not the case with pioglitazone, but various studies report that for pioglitazone the therapeutic level in the body is not achieved within 12 weeks of 30 mg pioglitazone. So comparing the efficacy of both groups at the end of phase A is not valid. The decrease in the glycemic profile is significant but none of the groups could achieve the healthy levels of the HbA1c required which is less than 7% [6].

This implies that the monotherapy is not sufficient in achieving the ideal profile while treating diabetes mellitus 2 in the moderate to high level of hyperglycemic, diabetic, obese and drug naïve patients. A similar finding has been reported in various studies [7]. There is a need for combination therapy when monotherapy fails to achieve the ideal levels.

In the phase B, patients had improved glycemic profiles from the previous therapy but ideal levels of HbA1c were achieved in both the groups at end of this phase. The fasting and post-prandial sugar levels were lowered significantly in both groups. Comparing the data from the two groups in Phase B it is clear that group 1 in Phase B had a more significant decrease than the other group that received pioglitazone. Group 1 received combination therapy which indicates that combination therapy has a better efficacy than monotherapy [8]. Group 2 in Phase B also showed an increase in the level of LDL and weight gain due to oedema was also reported. Whereas in group 1 of phase B, there was a decrease in weight and the lipid profile of the patients improved with combination therapy of sitagliptin and metformin [9].

The adverse drug reactions were numerically more in the group that received pioglitazone. However, the difference in the number of adverse drug reactions was not significant statistically and both the therapy was well tolerated and safe [10].

Conclusion

It can be concluded that to improve the glycemic profiles of the patients with moderate to high levels of glycaemia there is a requirement of combination therapy if monotherapy is not sufficient. From the study, it is obtained that the combination of sitagliptin and metformin, individual sitagliptin and individual pioglitazone has significant results. However, the combination therapy of sitagliptine and metformin is superior in treating type 2 diabetes mellitus in patients with moderate to high glycaemia, who received no treatment before and had a BMI greater than 30.

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