Original Article

Induction of Long-term Glycemic Control in Type 2 Diabetic Patients using Pioglitazone and Metformin Combination

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Abstract

Aims and Objective : To study the effects of pioglitazone and metformin combination in type 2 diabetics in achieving long-term optimal glycemic control.

Methods and Materials: Patients whose duration of type 2 diabetes was less than 24 months were selected for the study. 373 such patients meeting the selection criteria were included in the study and were started on triple drug combination therapy.

Results : Three hundred seventy three (183 females and 190 males) patients were initiated on a triple drug combination of gliclazide 80 mg, tid, metformin 500 mg tid and pioglitazone 30 mg od. Once controlled, the doses of gliclazide were reduced if the blood glucose levels decreased. Those patients whose plasma glucose remained in the normal range for more than 6 months without the use of a sulphonylurea were considered to be in pharmacological remission. 48 patients were lost to follow up. At the beginning of the study the pre treatment biochemical parameters in these 325 diabetic patients at the time of enrolment were : average FBG of 209.44±73.82 mg/dl, PLBG 294.96±107.58mg/dl, and HbA_{1c} 11.21±3.85. The post treatment glycemic parameters were: FBG was 124.38±40.48 mg/dl ($p < 0.0001$), and PLBG 162.32±54.33 mg/dl ($p < 0.001$), average glycosylated hemoglobin was 6.45±2.17 ($p < 0.001$). After using the triple drug combination pharmacological remission was achieved in 36.3 percent i.e. 118 (60 males and 58 females) patients. The average time required for achieving remission was 4 (±3.3) months in males and 5 (±4.02) months in females. 118 patients were maintained remission after 2 years of follow up. The average duration of remission is 27 (±2.66) months. There was an average weight gain of 2.56 ± 1.32 kg in both the groups of patients in remission and those who could not achieve remission.

Conclusions : In this study we have found that we could achieve long term glycemic control 'pharmacological remission' in 118 of the 325 patients i.e.36% of type 2 diabetic patients. Insulin sensitizers like pioglitazone along with metformin may induce long-term glycemic control in type 2 diabetic patients. ©

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly with 221 million cases predicted world-wide by the year 2010 with 41 millionAsian Indians already with the disease. The increasing risk of cardiovascular disease (CVD) two to four fold in T2DM is now the leading cause of blindness in working age adults, end-stage renal disease and non-traumatic lower extremity amputations. Even people with dysglycaemia, especially those with impaired glucose tolerance (IGT), are at increased risk of developing both CVD and T2DM.

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Recent studies, including the DPP,[1-3] STOP-NIDDM,[4,5] and Finnish DPS,[6,7] have shown that treating IGT subjects with lifestyle measures, acarbose or metformin can reduce their risk of developing T2DM. Two other studies, each using a different class of glucose-lowering agent, have shown a reduction in progression to diabetes with pharmacological intervention. In the Troglitazone in Prevention of Diabetes (TRIPOD) study[8] troglitazone treatment was associated with a 56% relative reduction in progression to diabetes. Of note, after a washout period of more than 8 months, the preventive effects of the drug were still observed. Thus, it is possible that troglitazone may affect the natural history of glucose intolerance and may actually prevent diabetes in some people rather than just delaying its onset.

In this study we were targeting patients of type 2 diabetes with duration of diabetes less than 24 months. The aim was to control their diabetes using a triple

drug combination of gliclazide 80 mg, tid, metformin 500 mg tid and pioglitazone 30 mg od. The study aims at seeing whether the continued use of metformin and pioglitazone can successfully prevent the relapse of diabetes and for how long.

Methods And Materials

373 cases of type 2 diabetes whose duration of diabetes was less than 24 months were selected for the study irrespective of the current mode of treatment. 373 such patients fitting the selection criteria were included in the study. The exclusion criteria were: patients with any cardiac abnormality, including history of symptomatic angina, cardiac insufficiency or history of myocardial infarction or an abnormal ECG, patients with known renal failure or increased Serum creatinine levels >1.5 mg/dl in males or > 1.4 mg% in females, patients with SGOT/SGPT more than 2 times the upper limit of normal, patients having more than 60 ml alcohol/day, patients of duration of diabetes of more than 24 months and patients currently on insulin therapy.

A total of 373 patients were enrolled meeting the inclusion criteria from Jan 2002 to Dec 2002. They were initiated on to a triple drug combination of gliclazide 80 mg tid with metformin 500 mg tid and pioglitazone 30 mg od. 48 patients were lost to follow up during the study leaving 325 evaluable patients, 166 males and159 females with average age 48.79 years and 48.38years respectively in the study.

All patients who met the inclusion criteria had their base line ECG, fasting and post prandial blood glucose, and HbA_{1c}, SGOT, SGPT, Creatinine and lipid profile done. Fasting and post lunch plasma glucose level and biochemical measures of safety, including chemistry tests (SGOT, SGPT), hematologic tests, were performed at 3-week, 1 month 2 months and subsequently 3 months intervals throughout the study. Self-monitoring of blood glucose level was done with glucose meters. At every follow-up the gliclazide doses were appropriately down titrated. Each patient was appropriately given education on hypoglycemia. Some patients who experienced hypoglycemia before the follow-up date were telephonically instructed to appropriately reduce or stop the dose of gliclazide. Those patients whose gliclazide was stopped continued to be on pioglitazone and metformin as started earlier. Repeat measurements of HbA_{1c} levels were done at 3 months, six months and every three months after that. Those patients who maintained euglycemia only on a combination of metformin and pioglitazone without any added sulphonylurea were considered to be in "pharmacological remission" after 6 months.

Results

Patients who maintained long-term optimal glycemic control (> 6 months) with only metformin and pioglitazone were called the "**remission**" group (118 of 325) **36%**; while those who continued to be on gliclazide in combination with metformin and pioglitazone were called the "**non-remission**" group (207of 325)

The pre treatment glycemic parameters of 325 diabetic patients at the time of enrolment were : average FBG of 209.44±73.82 mg/dl, PLBG 294.96±107.58mg/dl, and HbA_{1c} 11.21±3.85. The post treatment glycemic parameters were: FBG was 124.38±40.48 mg/dl, and PLBG 162.32±54.33 mg/dl, average glycosylated hemoglobin was 6.45±2.17. The Table 1 below is showing the comparison of data at the time of enrolment and at the time of analysis of the data.

Table 1 : Pre and post triple drug combination glycemic control data

	Pre Treatment	Post Treatment	p Value
Duration of DM	15.57±(9.29) months		
No.of patients	325	325	
BMI(Kg/M²)	26.28±4.21	27.31±4.23	>0.05
Weight	68.62±11.25	71.18±11.20	>0.05
FBG(mg/dl)	209.44±73.82	124.38±40.48	<0.0001
PLBG(mg/dl)	294.96±107.58	162.32±54.33	<0.0001
HbA1c %	11.21±3.85	6.45±2.17	<0.0001

At the beginning of the study the biochemical parameters in these 373 diabetic patients, were as follows: Males no. 190 average fasting plasma glucose 198.52 (SD±63.09) mg/dl, post lunch plasma glucose 281.67 (SD±95.05) mg/dl, and HbA_{1c} 10.67 (SD±3.37) mg/dl Females no 183 average fasting plasma glucose of 220.83(SD±82.23) mg/dl, post lunch plasma glucose 308.84(SD±117.97) mg/dl, and HbA1c 11.77 remission (SD±4.24) mg/dl).

118 of the 325 i.e. 36% of patients who maintained euglycemia only on a combination of metformin and pioglitazone without any added sulphonylurea were considered to be in pharmacological remission. The average time required for achieving remission in this study was 4 (±3.3) months in males and 5 (±4.02) months in females.

To determine patients who would most likely benefit from this treatment, we defined the patients who had long-term optimal glycemic control (> 6 months) with metformin and pioglitazone as the **remission** group (118 of 325) and those who continued to be on gliclazide in combination with metformin and pioglitazone as the **nonremission** group (207of 325).

There were no differences in age, BMI, FPG, PPG, HbA_{1c}, and lipid profiles between two groups at baseline.

As on April 2005, 118 patients were maintaining remission and are being followed up. The average duration of remission is 27 (±2.66) months. There was an average weight gain of 2.56 ± 1.32 kg in both the groups of patients in remission and those who could

not achieve remission.

Side effects: The obvious side effect of this combination is hypoglycemia. The patients were informed about the signs and symptoms of hypoglycemia and were told to immediately inform their doctor. In such cases the dosage of gliclazide was appropriately reduced.

Discussion

This study was primarily designed to validate the concept that once glutotoxicity settles down a combination of insulin sensitizers (metformin and glitazone) can sustain and maintain euglycemia in type 2 diabetes. Our group prefers to use the term pharmacological 'remission' for the group of patients who obtain, sustain and maintain euglycemia on sensitizer combination alone without the need of a secretagogues. This may appear controversial as some groups define 'remission' as euglycemia maintenance without pharmacotherapy. Independent of semantics we have predefined pharmacological remission 'as maintenance of euglycemia beyond 6 months only on insulin sensitizers without any other antihyperglycemic agent' in cases with type 2 diabetes.

This data does not apply to pre-diabetics or severe hyperglycemia subjects but to classical type 2 diabetics in the native Asian Indians. Lifestyle modification and metformin form the first line primary management in type 2 diabetes. Our current study attempts the use of glitazone to improve the glycemic status through its several published mechanisms via beta cell rest/neogenesis, reduction of glucotoxicity and lipotoxicity as well as its other pleotropic effects which are anti-inflammatory, anti-atherogenic and modulation of endothelial function. Most intriguing finding of metabolic memory/pharmaceutical memory which was observed with troglitazone in TRIPOD Study was the ability of the drug to sustain euglycemia after stoppage. This finding of glycemic memory could not be replicated by rosiglitazone washout in DREAM study.

The current study has 325 evaluable cases which were gender classified. We have termed the long term glycemic control group which was subsequently pulled off the secretagogues as the remission group. The glycemic control pre and post triple drug combination is listed in Table 1 and the impact of glycemic control in Table 2 with respect to our remission criteria. The purpose of the study was to demonstrate that early addition of pioglitazone ensured that once glucotoxicity was controlled by the secretagogue, the need for the same was obviated. This was due to the pleotropic effects of pioglitazone. Due to pioglitazone and metformin therapy long term maintenance of euglycemia is termed as 'remission'. The 'remission' term may appear a little aggressive.[11]

Currently monotherapy is unlikely to maintain glycemic control for more than a few years, combination therapy is becoming quite common. Fortunately, the presently available classes of agents have fully additive/synergistic therapeutic effects but independent side effects. The benefits of combining sulfonylureas with metformin,[12-14] sulfonylureas with troglitazone[15] and sulfonylureas with acarbose.[16,17] have been demonstrated long back. Recently consensus statement from the ADA and the European Association for the Study of Diabetes on the approach to management of hyperglycemia in individuals with type 2 diabetes has been published. This approach recommends early intervention with metformin in combination with lifestyle changes.[18] Second agent suggested is sulphonylurea or insulin. Though TZDs have not yet got their position in most of the gudelines, they have shown multiple beneficial effects in various drug trials.

Table 2 :

	Remission Group	Non Remission Group
No of patients	118	207
BMI (Kg/M^2)	28.00±4.22	26.91±4.21
Weight	72.97±10.44	70.16±11.51
FBG (mg/dl)	100.04±12.04	138.26±44.30
PLBG (mg/dl)	121.65±20.29	185.50±54.04
HbA_1c (mg/dl)	4.93±0.65	7.31±2.25
Duration of remission	27.01± 2.6 months	
Time Req. for remission	4.59± 3.74 months	

In patients with type 2 diabetes and the metabolic syndrome, the combinations of glimepiride with pioglitazone or rosiglitazone has shown significant improvements in measures of glycemic control, plasma lipids, and homocysteinemia.[19] Compared with metformin plus SU, addition of pioglitazone to SU resulted in a reduction of the urinary albumin-to-creatinine ratio and significantly greater improvements in triglyceride levels and HDL cholesterol levels.[20] As add-on therapy to existing sulphonylurea or metformin therapy, pioglitazone has shown to improve glycaemic control and this improvement was sustained over 2 years.[21,22] As a second line therapy in type 2 diabetic patients inadequately controlled on metformin monotherapy, add-on pioglitazone results in improvements in glycemic control comparable to that seen with glimepiride.[23] Compared to the established combination of metformin plus gliclazide, addition of pioglitazone to metformin has shown significant improvements in microalbuminuria and specific abnormalities associated with diabetic dyslipidemia.[24]

The co-formulation of pioglitazone and metformin is a rational approach that maximizes the established, complimentary benefits of these agents.[25] Such an approach of combining the distinct, but complementary, mechanisms of action of the thiazolidinediones and metformin has consequences, not only for improved

glucose control, but also for reducing metabolic risk and potentially improving major cardiovascular disease outcomes.[26] When used as part of triple oral therapy in patients with type 2 diabetes and secondary drug failure Pioglitazone is effective in achieving glycaemic targets and reducing risk factors involved in atherosclerosis and improving beta-cell function with 61% of patients achieving HbA_1c levels<6.5%.[27] In another Indian study with fixed dose triple drug combination similar beneficial effects in addition to pleotropic effects have been demonstrated.[28] Our own study showed that a triple drug combination of glibenclamide, metformin and pioglitazone resulted in significant reduction of insulin dose and documented the "insulin" saving effect of glitazones.[29]

In this study we have found that using a combination of pioglitazone and metformin we could achieve and maintain pharmacological remission in 118 of the 325 patients i.e. 36% of type 2 diabetic patients with average duration of Diabetes of 15.57±(9.29) months. The average time taken to induce remission was 4.59±3.74 months. The average duration of remission induced these patients was 27.01± 2.6 months. The mechanisms responsible for this **remission** could be due to a combination of two important modes of action of pioglitazone and metformin i.e. the improvement of β-cell function and increased insulin sensitivity.

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