STUDIES ON EFFICACY AND SAFETY OF GLIBENCLAMIDE AND PIOGLITAZONE DRUGS IN TYPE 11 NON-INSULIN DEPENDENT DIABETES MELLITUS PATIENTS

ABSTRACT:

OBJECTIVE: To evaluate the efficacy and safety of Glibenclamide and Pioglitazone drugs in type 11 non-insulin dependent diabetes mellitus patients.

STUDY DESIGN: study was prospective, randomized study.

PLACE AND DURATION: This study was conducted in the department of Pharmacology and Therapeutics, Muhammad Medical College Mirpurkhas, in collaboration with Medical Outpatient Department of Civil Hospital Dadu, Sindh

PATIENTS, METHOD: Hundred and twenty NIDDM (type-II) diabetic patients were enrolled in the study from the out patient department civil hospital Dadu. All the patients were divided in two groups.

RESULTS: In fasting blood sugar, the mean values of glibenclamide group at the start, six months were 150.5 ± 22.0, 92.2 ± 10.7 respectively, while that of Pioglitazone group were 150.5 ± 22.0, 101.7 ± 5.4 respectively. Therefore, the mean reduction of two hours postprandial blood glucose from the start till the end of the study (in 6th months) in glibenclamide group was 92.2 ±10.7 and pioglitazone was 101.7 ± 5.4 . Therefore, the mean reduction of HbA1c in the whole study in glibenclamide group was was 6.6 ± .9 and pioglitazone group was 7.4 ± .92 .All variables showed significant (P-value >0.05) when we compared between base line and 6 months study time period. In case of safety of drugs in glibenclamide 4.7% and pioglitazone 12% reactions were observed in the study.

CONCLUSION: In the light of this study it is obvious that glibenclamide was more effective, tolerable and safer than pioglitazone in a short duration of therapy.

KEY WORDS: Diabetes mellitus, Non-insulin diabetes mellitus, Insulin dependent diabetes mellitus, Glibenclamide, Pioglitazone, Insulin.

INTRODUCTION

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin. Type 2 diabetes mellitus is a group of disorders characterized by hyperglycemia and associated with microvascular (i.e., retinal, renal, possibly neuropathic), macrovascular (i.e., coronary, peripheral vascular), and neuropathic (i.e., autonomic, peripheral) complications. Unlike patients with type 1 diabetes mellitus, patients with type 2 are not absolutely dependent upon insulin for life, even though many of them are ultimately treated with insulin.

Hyperglycemia observed in diabetes mellitus results from inadequate glucose transport from the vasculature into cells of the liver and muscle.

Insulin is a hormone that regulates blood sugar. Hyperglycemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body’s systems, especially the nerves and blood vessels. It is associated with an impaired glucose cycle, altering metabolism.

People with type 2 diabetes have a deficiency of a hormone called insulin. Insulin is produced by the pancreas and is the main hormone responsible for controlling sugar levels in the blood. It normally makes the cells of the body remove excess sugar from the blood. In type 2 diabetes insulin is produced inefficiently in response to surges of blood sugar, e.g., following a meal. The cells of the body also become resistant to the action of insulin that is produced, which means that blood sugar levels can become too high. The World Health Organization (WHO) estimates that more than 180 million people worldwide have diabetes. This number is likely to be more than double by 2030. In 2005, an estimated 1.1 million people died from diabetes.1 Almost 80% of diabetes deaths occur in low and
middle-income countries. Almost half of diabetes deaths occur in people under the age of 70 years; 55% of diabetes deaths are in women. WHO projects that, diabetes deaths will increase by more than 50% in the next 10 years without urgent action. Most notably, diabetes deaths are projected to increase by over 80% in upper-middle income countries between 2006 and 2015.

Type 2 diabetes, formerly known as ‘non-insulin-dependent diabetes’ is caused by resistance to insulin combined with a failure to produce enough additional insulin to compensate for the insulin resistance. Type 2 diabetes represents approximately 90% of individuals with diabetes in the United States, while most of the remainder has type 1 diabetes.  

The prevalence of diabetes mellitus (DM) and impaired glucose tolerance (IGT) and the contributing risk factors were estimated by performing a cross-sectional survey conducted earlier in the rural and urban areas of all the four provinces of Pakistan. The statistical analysis was performed from the obtained results. The total number of subjects examined was 5433 which included 1893 males (1208 in rural and 685 in urban areas) and 3540 females (2243 in rural and 1297 in urban areas). The prevalence of diabetes in the urban versus the rural areas was 6.0% in men and 3.5% in women against 6.9% in men and 2.5% in women, respectively.

In Pakistan Insulin Dependent Diabetes Mellitus (IDDM) constitutes less than 2% of total Diabetic population. The other 98% suffer from Type II Diabetes. The prevalence of type I diabetes mellitus is highest in certain pacific island, intermediate in countries such as India and the United States, and relatively low in Russia and China. This variability is likely due to genetic, behavioral and environmental factors.

Diabetes mellitus prevalence also arises among different ethnic population within a given countries it is common in all ethnic groups its prevalence increased with age and more than 5% of individuals of more than 65 years of age have diabetes mellitus. Although newer agents have recently entered the marketplace, sulfonylureas still play a primary role in pharmacologic management of type 2 diabetes. Patients who respond best to treatment with sulfonylureas include those with a diagnosis of type 2 diabetes before 40 years of age, duration of disease less than five years before initiation of drug therapy and a fasting blood glucose level of less than 300 mg per dL (16.7 mmol perL). A combination of diet and exercise is known

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Glibenclamide</th>
<th>Pioglitazone</th>
<th>P.Value</th>
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<tbody>
<tr>
<td>Total No</td>
<td>60</td>
<td>60</td>
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<tr>
<td>Age of Patients</td>
<td>46.9 ± 7.0 year</td>
<td>46.4 ± 10.5 year</td>
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<tr>
<td>Weight of Patients</td>
<td>56.5 ± 10.4</td>
<td>56.3 ± 9.7</td>
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<tr>
<td>Body Mass Index</td>
<td>27.3 ± 3.8</td>
<td>29.8 ± 5.0</td>
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<tr>
<td>Fasting Blood Sugar</td>
<td>150.5 ± 22.0</td>
<td>154.0 ± 22.0</td>
<td></td>
</tr>
<tr>
<td>Gender of Patients M/F</td>
<td>48/12</td>
<td>38/22</td>
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<tr>
<td>Random Blood Sugar</td>
<td>266.0 ± 27.1</td>
<td>266.0 ± 27.1</td>
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</tr>
<tr>
<td>HbA1c</td>
<td>8.0 ± 1.1</td>
<td>8.0 ± 1.1</td>
<td></td>
</tr>
</tbody>
</table>

**EFFICACY OF BOTH DRUGS OF STUDY**

By Independent Sample T-test

**FIGURE 1**
to improve glycemic control in patients with type 2 diabetes, which in turn might improve beta cell function and enhance insulin action, and is the initial strategy for treatment. Unfortunately, 40-60% of patients do not achieve adequate glycemic control by these means alone. In these cases, oral hypoglycemic agents are added. Frequently used agents are the second generation sulfonylurea drugs glipizide and glibenclamide (glyburide), which increase insulin secretion by blocking the ATP-dependent potassium channel of the beta cells. The thiazolidinediones are a unique drug class of "insulin sensitizers" that promote skeletal muscle glucose uptake.

CAUSES OF HYPERGLYCEMIA AND ACTION OF ORAL ANTIDIABETIC AGENTS

Hepatotoxicity has been reported with pioglitazone, so liver function must be monitored every month for the first eight months of treatment and every other month for four months thereafter. Periodic transaminase measurements should be obtained as long as the patient is taking pioglitazone.

Pioglitazone is a drug that reduces the amount of glucose (sugar) in the blood. It is in a class of anti-diabetic drugs called "thiazolidinediones" that are used in the treatment of type II diabetes. Pioglitazone often is referred to as an "insulin sensitizer" because it attaches to the insulin receptors on cells throughout the body and causes the cells to become more sensitive (more responsive) to insulin. As a result, more glucose is removed from the blood. At least some insulin must be produced by the pancreas in order for pioglitazone to work.

Pioglitazone is prescribed once daily in doses ranging from 15 to 45 mg. Headache, fluid accumulation (edema) are common side effects of this drug.

RESEARCH DESIGN AND MATERIAL AND METHODS

This study was conducted in the department of Pharmacology and Therapeutics Muhammad Medical College Mirpurkhas in collaboration with Medical Outpatient Department of Civil Hospital Dadu, in the department of Pharmacology and Therapeutics. This study was conducted in the department of Pharmacology and Therapeutics, Muhammad Medical College Mirpurkhas, in collaboration with Medical Outpatient Department of Civil Hospital Dadu, Sindh.

Patients, Method: Hundred and twenty NIDDM (type-II) diabetic patients were enrolled in the study from the out patient department civil hospital Dadu. All the patients were divided in two groups.

Inclusion Criteria: Newly diagnose patients of non Insulin Dependent Diabetes Mellitus (type-11) Gender either Male or Female Age between 30 to 60 years


STUDY DESIGN: study was prospective, randomized study.

PLACE AND DURATION: This study was conducted from May 2008 to 31st December 2008. Base line blood sugar level checked.

RESULTS

Random Blood Sugar and HbA1c in both patients put on glibenclamide at the start level in glibenclamide group was 8.0 ± 1.1 and same value in pioglitazone group. Mean fasting glucose values of patients put on glibenclamide at the start of the study was 150.5 ± 22.0, and in pioglitazone group was 154.0 ± 22.0. Random Blood Sugar level at start of study in glibenclamide group was 266.0 ± 27.1, and same in pioglitazone group. HbA1c at start level in glibenclamide group was 8.0 ± 1.1 and same value in pioglitazone group. All values in mg/dl.

In fasting blood sugar, the mean values of blood glucose level at start of study in glibenclamide group at the start, six months from July 2008 to 31st December 2008. Base line criteria. Duration of study was 6 months from July 2008 to 31st December 2008. Base line blood sugar level checked.

DATA ANALYSIS PROCEDURE: Data was analyzed by SPSS 16. Mean ± SD was calculated for all quantitative variables like age, sex, BMI, Fasting blood sugar, Random Blood Sugar and HbA1c in both groups (Glibenclamide & Pioglitazone). Independent sample t-test was used to compare the mean age and FBS, RBS and HbA1c qualitative variables at 5% level of significance. Frequencies and percentages were calculated for all qualitative variables like gender, sex, body mass index (BMI), Fasting blood sugar (FBS), Random Blood Sugar (RBS) and HbA1c and adverse effect, compare the proportion of above mention. Results were presented in both graphs and tables.

RESULTS

One hundred and twenty cases of newly diagnosed type 2 patients were studied. Age range was 30 -60 years. Three basic parameters and any change in them were the basis of our study. They were fasting blood glucose, two hours postprandial blood glucose and mean values at the start, and at the end of one year were calculated. Mean fasting blood glucose values of patients put on glibenclamide at the start of the study was 150.5 ± 22.0, and in pioglitazone group was 154.0 ± 22.0. Random Blood Sugar level at start level in glibenclamide group was 266.0 ± 27.1, and same in pioglitazone group. HbA1c at start level in glibenclamide group was 8.0 ± 1.1 and same value in pioglitazone group. All values in mg/dl.

In fasting blood sugar, the mean values of glibenclamide group at the start, six months...
were 150.5 ± 22.0, 92.2 ± 10.7 respectively, while that of Pioglitazone group were 150.5 ± 22.0, 101.7 ± 5.4 respectively. Therefore, the mean reduction of two hours postprandial blood glucose from the start till the end of the study (in 6 months) in glibenclamide group was 92.2 ± 10.7 and pioglitazone was 101.7 ± 5.4. In two hours postprandial blood sugar, the mean values of glibenclamide group at the start and six months were 266.0 ± 27.1, 205.5 ± 17 respectively, while that of Pioglitazone group were 266.0 ± 27.1, 251.0 ± 25.6 respectively. Therefore, the mean reduction of two hours postprandial blood glucose from the start till the end of the study (in 6 months) in glibenclamide group was 205.5 ± 17.8 and pioglitazone was 251.0 ± 25.6. The glycosylated hemoglobin (HbA1c) was the most important parameter on which the efficacy of both the drugs depended. It showed a gradual decline in both the groups, especially in glibenclamide group at the start was 8.0 ± 1.1, at six months it was6.6 ± 9. In pioglitazone group the mean values of HbA1c at start, six months and one year were 8.0 ± 1.1 and 7.4 ± 9.2 respectively. Therefore, the mean reduction of HbA1c in the whole study in glibenclamide group was was6.6 ± 9 and pioglitazone group was7.4 ± 9.2 All variables showed significant (P-value > 0.05) when we compared between baseline and 6 months study time period. In case of safety of drugs in glibenclamide 4.7% and pioglitazone 12% reactions were observed in the study.

DISCUSSION
The treatment of type 2 diabetes patients is ever changing. New therapies are emerging each year to provide convenience and benefit to the patients regarding glycemic control and tolerability. One of the newer oral hypoglycemic agent is glibenclamide, which goes with the slogan, “One meal, one dose; no meal, no dose.” Our study was also designed to evaluate the safety and efficacy of glibenclamide and pioglitazone in the treatment of newly diagnosed type 2 diabetic patients. Three major parameters were chosen to evaluate the drugs. They were fasting blood glucose level, two hour post-parandial blood glucose, and glycosylated hemoglobin (HbA1c). All these results were compared with its baseline score of each group.

In fasting blood sugar, the mean values of glibenclamide group at the start, six months were 150.5 ±22.0, 92.2 ±10.7 respectively, while that of Pioglitazone group were 150.5 ± 22.0, 101.7 ± 5.4 respectively. Therefore, the mean reduction of two hours postprandial blood glucose from the start till the end of the study (in 6 months) in glibenclamide group was 92.2 ± 10.7 and pioglitazone was 101.7 ± 5.4. In two hours postprandial blood sugar, the mean values of glibenclamide group at the start, six months were 266.0 ± 27.1, 205.5 ± 17 respectively, while that of Pioglitazone group were 266.0 ± 27.1, 251.0 ± 25.6 respectively. Therefore, the mean reduction of two hours postprandial blood glucose from the start till the end of the study (in 6 months) in glibenclamide group was 205.5 ± 17.8 and pioglitazone was 251.0 ± 25.6. The glycosylated hemoglobin (HbA1c) was the most important parameter on which the efficacy of both the drugs depended. It showed a gradual decline in both the groups, especially in glibenclamide group at the start was 8.0 ± 1.1, at six months it was 6.6 ± 9. In pioglitazone group the mean values of HbA1c at start, six months and one year were 8.0 ± 1.1 and 7.4 ± 9.2 respectively. Therefore, the mean reduction of HbA1c in the whole study in glibenclamide group was was6.6 ± 9 and pioglitazone group was7.4 ± 9.2 All variables showed significant (P-value > 0.05) when we compared between baseline and 6 months study time period.

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REFERENCES
3) Dr. Raj Kumar, Ghulam Rasool Mashori “Comparison Hypoglycemic effects of Glibenclamide and Pioglitazone drugs in type 11 non- insulin dependent diabetes mellitus patients” 2007 on article base.com
6) JOE A. FLORENCE, M.D., and BRYAN F. YEAGER, PHARM.D. Treatment of Type 2 Diabetes Mellitus 1999 American Family Physician
9) Muhammad Ilyas Siddiqui Incidence and prevalence of such a devastating disease. The incidence of Diabetes globally, ... In Pakistan Insulin Dependent Diabetes Mellitus (IDDM)2009 http://www.weloveilmc.com/diseases/diabetes-pakistan.htm
11) Rushd Jibran1, M. Imran Suliman2, Fazayy Qurashi1, Masood Ahmed3 Safety and efficacy of Repaglinide compared with Glibenclamide in the management of type 2 diabetic Pakistani patients” 2006 Pak J Med Sci Vol. 22 No. 4 385-390
12) VERDICT & SUMMARY REFERENCES (VS08/08) Pioglitazone for the treatment of type 2 diabetes mellitus Date: March 2008 © Midlands Therapeutics Review & Advisory Committee VS08/08
13) Wikipedia, the free encyclopedia Diabetes mellitus type 2 2010 http://en.wikipedia.org/wiki/Diabetes_mellitus_type_2 Diabetes mellitus is a group of metabolic diseases characterized by high ... Diabetes mellitus, commonly referred to as diabetes (as it will be in this ..www.medicinenet.com › ... › diabetes mellitus index