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

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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: T*his study was conducted in the department of Pharmacololgy 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 was6.6 ± .9 and pioglitazone group was7.4 ± .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.[7]

Hyperglycemia observed in diabetes mellitus results from inadequate glucose transport from the vasculature into cells of the liver and muscle.[4]

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.[13]

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. [11]

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. [14].

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.[4]

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.[1]

In Pakistan Insulin Dependent Diabetes Mellitus (IDDM) constitutes less than 2 % of total Diabetic population. The other 98 % suffer from Type II Diabetes.[9]

The prevalence of type 11 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.[10]

Diabetes mellitus prevalence also arises among different ethic 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.2 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).[6]A combination of diet and exercise is known

TABLE-1
BASE LINE PARAMETERS OF STUDIED POPULATION

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

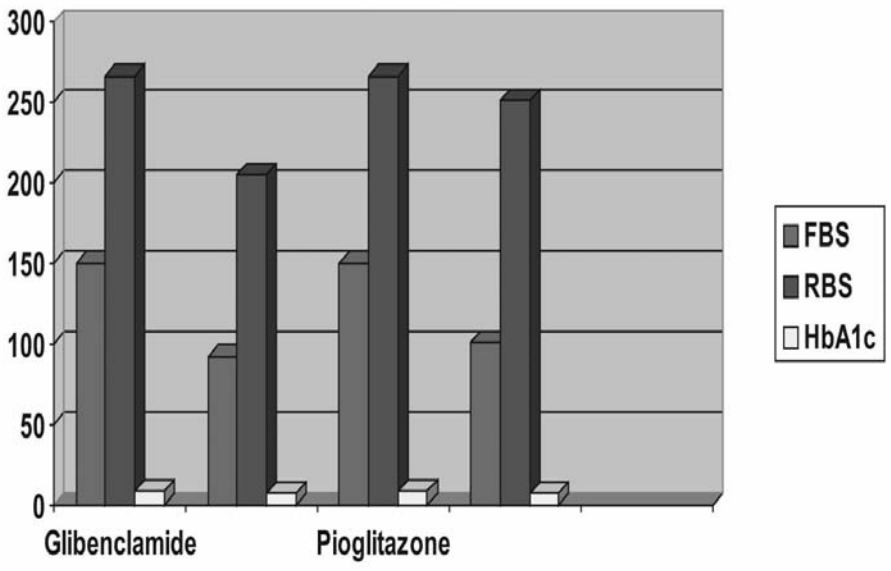
EFFICACY OF BOTH DRUGS OF STUDY

TABLE-2
COMPARISON OF BOTH DRUGS FROM ITS BASE LINE DATA

	Glibenclamide			Pioglitazone			
Parameters	Start	6 months	P.Value	Parameters	Start	6months	P.Value
Fasting Blood sugar	150.5 #22.00	92.2 #10.7	0. 002*	Fasting Blood sugar	150.5 #22.0	101.7 #5.4	0.003*
Random Blood sugar	266.0 #27.1	205.5 #17.8	0.001*	Random Blood sugar	266.0 #25.6		0.002*
HbA1c	8.0 #1.1	6.6 #.9	0.0007*	Hb1c	8.0 #1.1	7.4 #.92	0.007*

By Independent Sample T-test

FIGURE.1



to improve glycemic control in patients with type 2 diabetes,3 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 (glyburuide),1 which increase insulin secretion by blocking the ATP-dependent potassium channel of the beta cells.9 The thiazolidinediones are a unique drug class of "insulin sensitizers" that promote skeletal muscle glucose uptake.[6]

CAUSES OF HYPERGLYCEMIA AND ACTION OFORAL 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.6

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, sinusitis, muscle aches, tooth disorders, hypoglycemia, and sore throat. In addition, fluid accumulation (edema) are common side effects of this drug.5

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.

Hundred and twenty NIDDM (type-II) diabetic patients were initially enrolled in the study. All the patients were divided in two main groups, group I and II. Patients selected according to inclusion and exclusion criteria. Duration of study was 6 months from July 2008 to 31st December 2008. Base line blood sugar level checked.

TABLE-3
SAFETY OF BOTH DRUGS OF STUDY:

Side affects	Glibenclamide	Pioglitazone
GIT Disturbances	4.7%	7.2%
Hypoglycemia	0	0
Edema	0	1.8%
Sinusitis	0	3%
Total	4.7%	12%

STUDY DESIGN: study was prospective, randomized study.

PLACE AND DURATION: This study was conducted in the department of Pharmacololgy 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

EXCLUSION CRIRERIA:

Patients suffering from blood pressure. Patients suffering from liver disease. Patients suffering from cardiac disease. Pregnancies and lactating women. Patient suffering from renal disorders. Patients having serious complications of diabetes.

MATERIAL:

1.Glycosylated Hb A1c
Glucometer(Medisense) optilim one touch(Abbotts).
Blood glucose nest trpis (IVD for Invitro diagnostic use (Abbott Labortries,Medisense UK Ltd,Abigngdon,Ox14ITR,Masde in UK).
Stored between minimum 30C, (4°-30° C) and Maximum 40°C (39°-86°F).
Weight Machine Model No 1101 Lot No.312.
TANTIATA.
Drugs;Glibenclamide 30mg
Pioglitazone. 15-45mg PARAMETERS:
Fasting Blood Sugar (FBS).
Random Blood Sugar (RBS).Weight.

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 was 154.0 ± 22.0. Random blood glucose level at start of study in glibenclamide group was 266.0 ± 27.1, and same in pioglatazone group. HbA1c was 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 6th 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 6th 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 pioglatazone group the mean values of HbA1c at start, six months and one year were 8.0 ± 1.1 and 7.4 ± .92 respectively. Therefore, the mean reduction of HbA1c in the whole study in glibenclamide group was was6.6 ± .9 and pioglitazone group was7.4 ± .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.

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.[11]
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 6th months) in glibenclamide group was 92.2 ±10.7 and pioglitazone was 101.7± 5.4.
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In case of safety of drugs in glibenclamide 4.7% and pioglitazone 12% reactions were observed in the study.
Although long acting, glibenclamide is frequently given in split doses for type 2 diabetes mellitus. This may discourage compliance. It is thus appropriate to consider dosing it less frequently. Single daily dosing of glibenclamide was equivalent to multiple daily dose regimens. It can be used to an advantage to improve patient's compliance.[16]
Our study match with study of Dr Raj (2007), in this study the glibenclamide was more effective, tolerable and safer than pioglitazone in a short duration.[3]
The most common side effects seen in clinical trials with pioglitazone were upper respiratory tract infection, headache, sinusitis, muscle aches, tooth disorders, hypoglycemia, and sore throat. In addition, fluid accumulation (edema) occurred in less than 5% of patients taking pioglitazone.14No doubt its antidiabetic affects obvious but it produced more side effects as compared to glibenclamide in our study.
It is used in the treatment of type II diabetes. As of 2007, it is one of only two oral anti-diabetics in the World Health Organization Model List of Essential Medicines (the other being metformin). As of 2003, in the United States, it was the most popular sulfonyurea. [15]
Our study has shown that pioglitazone is effective and relatively safe drug, but foot edema and weight gain are of great concern to both the patient and the treating physician. Pioglitazone is a valuable in addition to the currently available oral antidiabetic agents. The efficacy of rosiglitazone 8 mg/d in improving glycaemic control in patients with type 2 diabetes is comparable to that of glibenclamide. However, rosiglitazone reduced insulin resistance and proinsulin levels whereas glibenclamide use was associated with an increase in fasting insulin and proinsulin. This suggests that in the long term, rosiglitazone may protect the beta-cell whereas glibenclamide is likely to increase the burden. But in our study glibenclamide was superior to pioglitazone in diabetes type 2.8
One RCT (PROactive study5) used a combined clinical endpoint as the primary outcome; all others used the reduction in plasma glycosylated haemoglobin concentration (HbA1 c) as a measure of glycaemic control. All clinical trials described below were carried out in adult patients with type 2 diabetes.
In the PROactive study, 5 pioglitazone was compared with placebo in 5,238 patients who had evidence of extensive macrovascular disease. Patients continued their existing antidiabetic medication (metformin or a sulphonylurea or both, with or without insulin). The trial had a mean follow-up period of 34.5 months. Results showed no significant difference between pioglitazone and placebo (p = 0.095) for the primary outcome, which was a composite of: death from any cause, non-fatal MI, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. For the secondary endpoint, a composite of death from any cause, non-fatal MI or stroke, there were significantly fewer events with pioglitazone treatment Compared with placebo: HR 0.84 (95% CI 0.72 to 0.98, p = 0.027). [12]
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REFERENCES

1) A Shera, F. Jawad, A. Maqsood Prevalence of diabetes in Pakistan2009 Diabetes Research and Clinical Practice, Volume 76, Issue 2, Pages 219-222.
2) David Owerback NJ-Prevalence in diabetes population-Diabetes 1988,02(6) :31-32.
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
4) D.TGraves, R. Liu, M. Alikhani, H. Al-Mashat and P.C. Trackman Diabetes-enhanced Inflammation and Apoptosis—Impact on Periodontal (2006) Pathology Journal of Dental Research, Vol. 85, No. 1, 15-21 DOI: 10.1177/15440591 0608500103
5) Jay Marks, "Pioglitazone" 2007 Online available athttp://www.medicinenet.com/pioglitazone/page2.htm
6) JOE A. FLORENCE, M.D., and BRYAN F. YEAGER, PHARM.D. Treatment of Type 2 Diabetes Mellitus 1999 American Family Physian
7) Kenneth Patrick L Ligaray, William L Isley, "Diabetes Mellitus, Type 2: Treatment & Medication 2010.AVAILABLE ON LINE AT http://emedicine.medscape.com/article/117853-treatment
8) Markolf Hanefeld, Rita Patwardhan, Nigel P Jones, Rosiglitazone Clinical Trials Study Group. A one-year study comparing the efficacy and safety of rosiglitazone and glibenclamide in the treatment of type 2 diabetes. Nutrition metabolism, and cardiovascular., diseases : NMCD. 2007 17 (1) 13-23.
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.welovelmc.com/diseases/diabetes pakistan.htm
10) Power AC-Epidemiology of type11 diabetes Basic facts of diabetes –Diabetes 2005;1(1)7-9
11) Rushd Jibran[1], M. Imran Suliman[2], Fayyaz Qureshi[3], Masood Ahmed[4]' Safety and efficay 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
14) WHO "Diabetes" 2002 http://www.who.int/diabetes/en/
15) WHO (March 2007) Model List of Essential MedicinesPDF (612 KiB), 15th edition, World Health Organization, p. 21. Retrieved on 2007-11-19.
16) W.Wan Mohamad "Efficacy and safety of single versus multiple daily doses of glibenclamide in type 2 diabetes mellitus. 2009 Diabetes Research and Clinical Practice, Volume 49, Issue 2, Pages 93-99.