SAFETY AND EFFICAY OF REPAGLINIDE COMPARED WITH GLIBENCLAMIDE IN THE MANAGEMENT OF TYPE 2 DIABETIC PAKISTANI PATIENTS

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ABSTRACT

Objective: To evaluate the safety and efficacy (glycemic control) provided by repaglinide compared with glibenclamide in newly diagnosed type 2 (non-insulin dependant) diabetic patients.

Settings: Diabetic clinic in medical outdoor of Mayo Hospital, Lahore.

Design: Randomized prospective study.

Methods: This single center study of one year duration was carried out in 100 patients between 30-70 years, all diagnosed to have type 2 diabetes mellitus recently and were not on any treatment. They were randomly categorized into two groups, repaglinide (test) and glibenclamide (control) groups. The study consisted of an initial induction day followed by follow-up visits after every fortnight. Repaglinide was given pre-parandial up to three times a day and glibenclamide was administered once or twice daily. Dosage was adjusted after every visit according to blood glucose level. Fasting blood glucose level, two hours postparandial blood glucose, weight and blood pressure were recorded on every visit, while glycosylated hemoglobin (HbA1c) was estimated thrice during the study (at the beginning, at six months and at the end of one year).

Results: Of the hundred randomized patients (50 in each groups), all showed a decrease in fasting blood glucose level, two hours postparandial blood glucose and HbA1c. Mean reduction in fasting blood glucose in repaglinide group was 64±53 mg/dl and those by glibenclamide group was 34.7±53 (P=0.007). The mean reduction in two hours postprandial blood glucose was 119±66 in repaglinide group, while 87.6±74 was observed in glibenclamide group (P=0.02). HbA1c mean reduction in both repaglinide and glibenclamide groups was 1.1±0.3 and 0.7±0.5 respectively (P=0.00). No statistically significant weight change was observed and no hypoglycemic events were recorded in both the groups.

Conclusion: The results suggest that repaglinide and glibenclamide both were effective in lowering fasting glucose level, two hours postparandial blood glucose level and HbA1c if used regularly for one year. The effect of repaglinide in lowering HbA1c was impressive as compared to glibenclamide. Both the drugs were well tolerated and weight change was minimal in both the groups.

KEY WORDS: Repaglinide, Glibenclamide, Type 2 diabetes mellitus, Glycosylated haemoglbin, HbA1c.

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INTRODUCTION

Type 2 (non-insulin dependant) diabetes mellitus is characterized by impaired insulin secretion and insulin resistance.[1,2] Defects in insulin secretion include impairment or loss of first phase response to intravenous glucose, delayed and reduced meals, and alteration in the normal pulsatile secretion of insulin.[1] As the beta cell dysfunction progresses, these defects eventually lead to overt hyperglycemia, which may require pharmacological treatment.

A combination of diet and exercise is known 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 avoided. Frequently used agents are the second generation sulfonylurea drugs glipizide and glibenclamide (glyburuide),[4] which increase insulin secretion by blocking the ATP-dependent potassium channel of the beta cells.[5] However, about 20-25% of type 2 diabetic patients are unresponsive to these agents (primary failure). And an additional 5-10% of patients each year eventually become unresponsive (secondary failure).[6]

Another major disadvantage of sulfonylureas is hypoglycemia, which occur in a significant proportion of patients. In up to 20% of the patients treated for six months, mild hypoglycemia develops,[7] while the incidence of severe hypoglycemic episodes is approximately 0.2/1000 patient year[8] that appears to be greater with long acting agents, such as glibenclamide and chlorpropamide, than with short acting agents.[9,10]

Repaglinide is a new oral hypoglycemic agent for the treatment of type 2 diabetes. Repaglinide is the first member of carbamoylmethylbenzoic acid family to be used in a clinical setting and represents a new class of insulin secretagouges. Repaglinide stimulates insulin secretion from the pancreatic beta cells by closure of the ATP-sensitive potassium channel via a different binding site to the sulfonylurea, and differs further in its mechanism of action and its mode of excretion.[11] In healthy volunteers, repaglinide is rapidly absorbed and almost completely metabolized by the liver to pharmacologically inactive derivatives. Repaglinide is predominantly excreted via the bile into the feces, with a plasma half life of less than one hour,[12] and hence the risk of hypoglycemia, and in particular, severe, long standing hypoglycemia, would be expected to be low during treatment with repaglinide. Its rapid elimination and route of excretion make repaglinide suitable for use in type 2 diabetic patients with sufficient beta cell function.

In clinical trial, repaglinide has been shown to produce comparable glycemic control to sulfonylureas.[12-15] A study with repaglinide has shown that preparandial dosing is associated with better glycemic control than three times daily dosing postparandial with the same total dose.[16] Hence, because of its short pharmacokinetic profile, repaglinide has been developed to specifically target meal-related requirements in type 2 diabetes. We designed this study to check its efficacy in Pakistani population.

PATIENTS AND METHODS

This randomized prospective study of one year duration (Aug 2000-July 2001) was carried out in hundred patients both male and female between 30-70 years visiting diabetic clinic in medical outdoor of Mayo hospital, Lahore. All of these patients were newly diagnosed and had come for the first time to the "diabetic clinic" to seek medical treatment. After informed consent the patients were categorized into two groups. One group was termed as Repaglinide group (test) and the other as glibenclamide group (control). Fifty patients were randomly selected for each group. Evaluation of the patients involved the following steps:

1. *History*: Personal details like age, sex, occupation, address and telephone numbers were recorded. In addition to family history of diabetes mellitus, personal history with drug history was also taken. Usual symptoms which had compelled the patients to seek advice (symptoms at presentation) were also noted. They included polyuria, polydypsia, polyphagia, headache, dizziness, fatigue, lethargy, body aches and pains. Symptoms due to complications of diabetes mellitus like palpitations, chest pain, dypnoea, facial puffiness, transient ischemic attack, burning sensation, numbness of extremities and blurred vision were also asked for. This was done to rule out

undiagnosed long standing diabetes mellitus. Any coexistant disease was looked for. None of the patients had any other major illness and were not taking any long term medication.

2. *Physical Examination*: It included weight in kilograms and height in meters. Systolic and diastolic blood pressures were recorded. Examination of CNS to assess the state of cranial nerves, motor, sensory and cerebeller systems was performed. Ophthalmoscopy was done to rule out any diabetic retinal complications. Examinations of CVS included assessment for edema and peripheral pulses.

3. *Investigations*: Following investigations were carried out in all patients at the start (day one) of the study. They included fasting blood sugar, two hours postparandial blood glucose, HbA1c, serum urea and creatinine level.

Follow up: The study was designed with the follow-up visits after every fortnight. On such visits parameters like fasting blood glucose, two hours postparandial blood glucose, body weight in kilograms and blood pressure (systolic/diastolic) were evaluated.

Body mass index (BMI) of patients on each visit was later calculated according to the formula (BMI=kg/m^2). Blood glucose was monitored by using "one touch glucose analyzer" which was correctly calibrated using mg/dl. Blood pressure was measured by using sphygmomanometer with appropriate cuff size. HbA1c was evaluated again after six months and at the end of one year study period. All of the results of the parameters (discussed above) were filled on a proforma specially designed for the study. Repaglinide was used as the only antidiabetic drug in half of the subjects (termed as repaglinide group; N=50), starting with a low dose of 0.5mg three times a day, at any time from thirty minutes to immediately before a meal, and titrated to a maximum dose of 2mg thrice a day based on blood glucose levels.

Glibenclamide was used as the only antidiabetic drug in the other half (termed as glibenclamide group, N=50) which acted as a control group. Glibenclamide was started as 5mg/day and titrated upwards. A maximum of 15mg/day was administered. In either group the aim was to achieve fasting blood glucose of <130 mg/dl and postprandial blood glucose of <175 mg/dl.

During the study period all patients were treated with individualized weight maintaining diet (carbohydrates 55-60%, fat 30% and proteins 12-20%) with the caloric content adjusted according to the patients age, body weight and physical activity (as recommended by the dietitian). Patients were also motivated to keep their nutritional habits, physical activity and general life styles as constant as possible. The safety and tolerability profiles of the drugs were investigated on the patients' reports of adverse events and by review of the laboratory test results. On every visit the patients were asked about any side-effects of the drug they were taking. Symptoms of hypoglycemia (palpitations, nausea, sweating, dizziness, headache, etc.) were specially asked for. The compliance with the drugs (repaglinide and glibenclamide) was sometimes assessed by counting of tablets used weekly.

Statistical Analysis: The data from the filled proformas was entered in a computer spread sheet and calculations were made by using SPSS software (version 10.0). Conclusions regarding safety and efficacy were drawn by comparing the results of the study patients with those of the control group. Student t-test was applied to find the significance of difference observed in the two study populations.

Inclusion Criteria: All newly diagnosed type 2 diabetic patients who remained uncontrolled after diet and exercise.

Exclusion Criteria: Patients of type 1 diabetes mellitus, type 2 patients who are already

Table–I: Baseline parameters of
the studied population

Parameters	Glibenclamide	Repaglinide
Total no.	50	50
Age	45.8±8.8	46.6±10.5
M/F (No.)	10/40	16/34
Weight (kg)	65.8±9.4	72.7±17
Height (m)	1.6±0.5	1.54±0.5
BMI	30.4±5.6	27.1±3.5

taking maximum or near maximum doses of sulfonylureas and whose diabetes was still not controlled (patients with secondary failure), type 2 diabetic patients already on insulin, and patients taking diabetogenic drug were not included in the study. Moreover, patients having significant gastrointestinal, cardiovascular, or renal disease by history, physical examination or laboratory evidence or having concurrent medical illness requiring immediate treatment were also excluded from the study.

RESULTS

One hundred cases of newly diagnosed type 2 patients were studied. All of them were between 30 years to a maximum of 70 years of age. In the glibenclamide group, the mean age was 45.8±8.8 years, while in the repaglinide group the mean age was 46.6±10.5 years, as mentioned in Table-I. Male to male ratio was different in both groups. In glibenclamide group (N=50), 10 were males (20%) and 40 were females (80%), while in the repaglinide group (N=50), 16 were males (32%) and 34 were females (68%). On the whole there were 26% males and 74% females in the study. The mean weight of repaglinide group was 65.8±9.4 kilograms, while that of repaglinide group was 72.7±17 The mean height of the patients in glibenclamide group was 1.6±0.5 m, while that of repaglinide group was 1.54±0.5. Body mass index (BMI) of glibenclamide and repaglinide groups was 30.4±5.6 and 27.1±3.5 respectively. All these observations are tabulated in Table-I. In repaglinide group the mean dosage used was 4.27 mg/day and in glibenclamide group it was 8.8 mg/day.

Four basic parameters and any change in them were the basis of our study. They were fasting blood glucose, two hours postprandial blood glucose. HbA1c and weight. The mean values at the start, six months and at the end of one year of both the groups were calculated. Mean fasting blood glucose values of patients put on repaglinide at the start of the study was 171±53, at six months 124±26 and at the end of one year, it was 106±11. In glibenclamide group, at the start it was 140±56, at six months 116±18 and at the end of one year 105±12.7. All values in mg/dl. Therefore, the mean reduction of fasting blood glucose level in repaglinide group was 64±53 and glibenclamide34.7±53 (P=0.007) (Table–II & III).

In two hours postprandial blood sugar, the mean values of repaglinide group at the start, six months and the end of one year were 267±73, 192±42 and 147±23 respectively, while that of glibenclamide group were 229.6±79, 178±40 and 142±25 respectively. Therefore, the mean reduction of two hours postprandial blood glucose from the start till the end of the study (in one year) in repaglinide group was 119±66 and glibenclamide was 87.6±74(P=0.02).

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 repaglinide group at the start was 9.9±1.6, at six months it was 9.3±1.6 and at the end of one year it was 8.8±1.7. In glibenclamide group the mean values of HbA1c at start, six months and one year were 10.2±1.6, 9.8±1.6 and 9.4±1.5 respectively. Therefore, the mean reduction of HbA1c in the whole one year in repaglinide group was 1.1±0.3 and glibenclamide group was 0.7±0.5 (P=0.001).

Table–II: Comparison of mean values of the two drugs

	Repaglinide group			Glibenclamide		
Parameters	*Start*	*6months*	*1year*	*Start*	*6months*	*1year*
Blood sugar fasting	171±53	124±26	106±11	140±56	116±18	105±12.7
2hrs pp Blood sugar	267±73	192±42	147±23	229.6±79	178±40	142±25
HbA1c	9.9±1.6	9.3±1.6	8.8±1.7	10.2±1.6	9.8±1.6	9.4±1.5
Weight (Kg)	65.8±9.4	66±9.4	66±8.8	72.7+17.4	72.7±16.5	71.7±15.2

Table-III: Mean reduction of fasting blood glucose, 2hours postprandial blood glucose and HbA1c by the two drugs

Parameters	Repaglinide	Glibenclamide	P-value
Fast Blood Sugar (mg/dl)	64±53	34.7±53	.007
2hrs pp Blood sugar (mg/dl)	119±66	87.6±74	.02
HbA1c (%)	1.1±0.3	0.7±0.5	0.00

The mean weight on the whole remained steady. There was a statistical insignificant increase in the mean weight of patients in repaglinide group. There was no change in weight of patients in glibenclamide group. The mean weight in repaglinide group at the start, six months and at one year was 65.8±9.4, 66±8.8 respectively, while that of glibenclamide group was 72.7±17.4, 72.2±16.5 and 71.7±15.2 respectively. Therefore, the mean gain and reduction of weight in the whole study in repaglinide group was 0.4±3.2. The P value was not significant.

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 repaglinide, 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 repaglinide in the treatment of newly diagnosed type 2 diabetic patients. Four major parameters were chosen to evaluate the drugs. They were fasting blood glucose level, two hour post-parandial blood glucose, glycosylated hemoglobin (HbA1c) and weight. All these results were compared with a group of patients taking glibenclamide, (which was to act as control) which is considered as a gold standard in the treatment of type 2 diabetic patients.

The results of our study can be compared with many international studies. The decrease in HbA1c by 1.1±0.3 (P=0.001) is impressive in repaglinide group. There is a decrease in HbA1c in patients taking glibenclamide, but it is more significant in patients who were on repaglinide. These results are comparable with a study by Goldberg RB, et al (15) which showed a decrease in HbA1c in patients on repaglinide from 8.5 to 7.8% with a statistically significant difference of 0.7% (P<0.0001). In another study by Owens,[17] repaglinide decreased HbA1c by 1.8 % as compared with glibenclamide counterpart, and is consistent with our findings. One study [127] showed a similar decrease in HbA1c % by both glibenclamide and repaglinide by 1.0%. Two other studies by Jovanovich[18] and Moses[19] have proven a decrease in HbA1c by 1.8% and 1.4% respectively using repaglinide.

By the end of the study, the fasting blood glucose values were lower in the repaglinide group than in the glibenclamide group with a difference approaching statistical significance (repaglinide-64±53 and glibenclamide 34.7±53; P=0.007). Similarly, two hours postprandial blood glucose level showed greater reduction by repaglinide as compared to glibenclamide, also depicting a statistically significant difference (Repaglinide- 119± 66 and glibenclamide 87.6 ± 74; P=0.02). These findings are consistent with the study by Landgraf[20] which showed a decrease in fasting blood glucose and two hours postparandial blood glucose with a statistical significance.

Repaglinide and glibenclamide were both well tolerated. No significant difference was observed between the two treatment groups with respect to adverse events, including hypoglycemic episodes and weight changes.

CONCLUSION

The conclusions drawn from our study are as follows:

1. Repaglinide and glibenclamide were both well tolerated.
2. They were both effective in lowering fasting blood glucose, two hours postparandial blood glucose and HbA1c if used regularly for one year.
3. Repaglinide was more effective in lowering all the three parameters. The effect on HbA1c was most impressive.

4. Weight gain was minimal over a period of one year.

The study shows that repaglinide is as effective as the other treatments of type 2 diabetes mellitus, which are considered as gold standard e.g., glibenclamide. Morever, repaglinide is convenient to use, allowing patients to adjust their medication around their meals and not meals around their medications. However larger study for a longer period of time is required to evaluate its importance in reducing the complications of diabetes.

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