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Retraction Announcement

The following manuscript has been retracted from issue January March, 2011 because of ethical misconduct which was detected later. **Editor**
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Comparison of Repaglinide with Glibenclamide in the Reduction of HBA1C of Type 2 Diabetic Patients

KHURRAM SALEEM, MOHAMMAD ALI YASIN[1], ANSER ASRAR[2], *SAMINA QAMAR*
Department of Medicine, King Edward Medical University/ Mayo Hospital, Lahore
[1] Social Security Hospital, Okara
[2]Deptt. Of Physiology, Lahore Medical & Dental College
Correspondence to Dr. Khurram Saleem, Senior Registrar Email: khurramsaleem@hotmail.com

ABSTRACT

Objective: To evaluate the efficacy (glycemic control/HbA1C)) provided by repaglinide compared with glibenclamide in type 2 diabetic patients.
Research Design & Methods: This single-center, randomized prospective study of one year duration was carried out in 100 patients aging 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. Repaglinide was given preprandially upto three times a day and glibenclamide was administered once or twice daily. Dosage was adjusted according to blood glucose level. Fasting blood glucose, two hours postprandial blood glucose, weight and blood pressure was recorded on every visit, while (HbA1c) was done 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 group), all showed a decrease in fasting blood glucose, two hours postprandial blood glucose and HbA1c. Mean reduction in fasting blood glucose by repaglinide group was 64 ± 53 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=0.000). No statistically significant weight change was observed and no hypoglycaemic event was recorded in both the groups.
Conclusion: The results suggest that repaglinide and glibenclamide both were effective in lowering fasting, two hours postprandial blood glucose 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 groups.
Key words: Repaglinide, glibenclamide, type 2 diabetes mellitus, HbA1c

INTRODUCTION

The control of type 2 diabetes in Pakistan remains unsatisfactory. The United Kingdom Prospective Diabetes Study (UKPDS) believes that improved control of type 2 diabetes can be helpful in ameliorating the substantial morbidity associated with the disease. However, controversy still exists over the appropriate choice of therapy. On average sulfonylurea therapy reduces fasting plasma glucose by 50-70 mg/dl and reduces HbA1c by 0.8-1.7%(6,8,13). However, sulfonylureas differ in their relative potency, duration of action, and side effect profile, allowing one to choose the most appropriate agent for a specific patient.(9,10)

Repaglinide is a meglitinide analogue. It acts by binding to sulfonylurea receptor and closing the ATP-sensitive potassium channel.(1,2,11).It is rapidly absorbed from the intestine and then undergoes complete metabolism in the liver to inactivate biliary products giving it a plasma half life of less than one hour. The drug therefore causes a brief but rapid pulse of insulin. Our aim was to compare the two drugs.(7,12,13)

MATERIAL & METHODS

This randomized prospective study of one year duration (March 2006-March.2007) was carried out in hundred patients both male and female aging 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 "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). 50 patients were randomly selected for each group. Evaluation of the patients involved the following steps:

1. History:
2. Physical Examination.
3. Investigations:

Following investigations were carried out in all the patients at the start (day one) of the study. They included: Fasting blood glucose, two hours postprandial blood glucose, HbA1c, Urea, Creatinine

Follow-up: The study was designed with follow-up visits after every fortnight. On each visit following parameters were evaluated: Fasting blood glucose, 2 hours postprandial blood glucose, Body weight in kilograms, Blood pressure (systolic/diastolic) and BMI (KG/M2)

HbA1c was evaluated again after six months and at the end of one year study. In either group the aim was to achieve fasting blood glucose of < 130mg/dl and postprandial blood glucose of < 175mg/dl.

Statistical Analysis: The data from the filled proformas was entered in a computer spread sheet and calculations were made using SPSS software (version 10.0). Conclusions regarding safety and efficacy were drawn by comparing the results of the udy patients with those of the control group. Student's 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:

- Type 1 diabetic patients
- Type 2 patients patients who are already taking maximum or near minimum doses of sulfonylureas and whose diabetes was still not controlled (patients with secondary failure).
- Type 2 diabetic patients already on insulin.
- Patients having significant gastrointestinal, cardiovascular, or renal disease by history, physical examination or laboratory evidence.
- Concurrent medical illness requiring immediate treatment.

RESULTS

One hundred cases of newly diagnosed type 2 patients were studied. All of them were having age greater than 30 years to a maximum of 70 years. 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 5.

Male to female 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 (Table 5).

The mean weight of glibenclamide group was 65.8 ± 9.4 kilogram, while that of repaglinide group was 72.7±17 (Table 1). The mean height of the patients in glibenclamide group was 1.6± 0.5m, while that of repaglinide group was 1.54±0.5 (Table 1). 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 1. In repaglinide group the mean dosage used was 4.27mg/day and in glibenclamide group it was 8.8mg/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 are given below (Table 2). 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. Therefore, the mean reduction of fasting blood glucose level in repaglinide group was 64±53 and glibenclamide 34.7± 53 (P=0.007) (Table 2 & 3).

Table 1: 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

In 2 hours postprandial blood sugar, the mean values of repaglinide group at the start, six months and at 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 group was 87.6 ± 74 (P= 0.02). The glycosylated haemogloin (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. The mean HbA1c of the patients 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 = .000). The mean weight on the whole remained steady. The P value was not significant (Table 6,7).

Table 2: Comparison of Mean Values- blood sugar of the Two Drugs

Repaglinide Group			
Parameters	**Start**	**6 Months**	**1 Year**
Blood sugar fasting	171±53	124±26	106±11
2hrs pp Blood sugar	267±73	192±42	147±23
HbA1c	9.9±1.6	9.3±1.6	8.8±1.7
Weight (kg)	65.8±9.4	66±9.4	66±8.8
GlibenclamideGroup			
Start	**6 Months**	**1 Year**	
140 ± 56	116 ± 18	105 ± 12.7	
229.6 ± 79	178 ± 40	142 ± 25	
10.2 ± 1.6	9.8 ± 1.6	9.4 ±1.5	
72.7 ± 17.4	72.2 ± 16.5	71.7 ±15.2	

Table 3: Mean reduction of fasting blood glucose, 2 hours postprandial blood glucose and HbA1c by the two drugs

Parameters	**Repa-glinide**	**Glibencla -mide**	**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	.000

DISCUSSION

The results of our study can be compared with many international studies. The decrease in HbA1c by 1.1±0.3 (P=0.000) is impressive in the repaglinide group. Though 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[4,14] 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,[3] repaglinide decreased HbA1c by 1.8% as compared with glibenclamide counterpart, and is consistent with our findings. Two other studies showed a similar decrease in HbA1c % by both glibenclamide and repaglinide by 1.0% during Ramadan(17). Two other studies by Jovanovich and Moses [15] have proven a decrease in HbA1c by 1.8% and 1.4% respectively 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 has also been reduced by repaglinide more 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([16] which showed a decrease in fasting blood glucose and two hours postprandial blood glucose with a statistical significance. Repaglinide and glibenclamide were both well tolerated. No significant differences were observed between the two treatment groups with respect to adverse events, including hypoglycaemic episodes and weight change.

CONCLUSIONS

1. Repaglinide and glibenclamide were both well tolerated.
2. They were both effective in lowering fasting blood glucose, two hours postprandial 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 this new hypoglycaemic agent (repaglinide) is as effective as the other treatments of type 2 diabetes mellitus, which are considered as gold standard e.g. glibenclamide. However, repaglinide is convenient to use, allowing patients to adjust their medication around their meals and not meals around their medication..

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