ORIGINAL ARTICLE

A Comparative Study of Repaglinide & Glibenclamide in Type 2 Diabetic 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 dependent) diabetic patients.

Study Design: This single-center, randomized prospective study of one year duration was carried out in two hundred patients aging between 30-65 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 preprandially upto 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, two hours postprandial blood glucose, weight and blood pressure was recorded on every visit.

Results: Of the two hundred randomized patients (100 in each group), all showed a decrease in fasting blood glucose and two hours postprandial blood glucose. Mean reduction in fasting blood glucose by repaglinide group was 63±52 and those by glibenclamide group was 34.2 ± 52 (P=0.006). The mean reduction in two hours postprandial blood glucose was 118 ± 68 in repaglinide group, while 88.0±73 was observed in glibenclamide group (P=0.03). 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 and two hours postprandial blood glucose if used regularly for one year. Both the drugs were well tolerated and weight change was minimal in both groups.

Key words: Repaglinide, glibenclamide, type 2 diabetes mellitus, glycosylated haemoglobin

INTRODUCTION

Type 2 (non-insulin dependent) diabetes mellitus is characterized by impaired insulin secretion and insulin resistance[1,2]. Defects in insulin secretion include impairment or loss of the 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 hyperglycaemia, which may require pharmacological treatment.

A combination of diet and exercise is known to improve glycaemic 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 glycaemic control by these means alone. In these cases, oral hypoglycaemic agents are used. Frequently used agents are the second-generation sulfonylurea drugs glipizide and glibenclamide (glyburide)[4], which increases insulin secretion by blocking the ATP-dependent potassium channel of the beta-cells. 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)[5]. Another major disadvantage of sulfonylureas is hypoglycaemia, which occur in a significant proportion of patients. In up to 20% of patients treated for six months, mild hypoglycaemia develops[6], while the incidence of severe hypoglycaemic episodes is approximately 0.2/1000 patient-years[7,8]. The incidence of hypoglycaemia appears to be greater with long acting agents, such as glibenclamide and chlorpropamide, than with short acting agents[9].

Repaglinide is a new oral hypoglycaemic agent for the treatment of type 2 diabetes. Repaglinide is the first member of the carbamoylmethylbenzoic acid family to be used in a clinical setting and represents a new class of insulin secretagogues. Repaglinide stimulates insulin secretion from the pancreatic beta cells by closer of the ATP sensitive potassium channel via a different binding site to the sulfonylurea, and differs further in its mechanism of

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action and its mode of excretion[10]. In healthy volunteers, repaglinide is rapidly absorbed and almost completely metabolized by the liver to pharmacologically inactive derivatives[11]. 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 hypoglycaemia, and in particular, severe, long standing hypoglycaemia, 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 trials, repaglinide has been shown to produce comparable glycaemic control to sulfonylureas[12]. A study with repaglinide has shown that preprandial dosing three times daily is associated with better glycaemic control than twice daily dosing with the same total dose. Hence, because of its short pharmacokinetic profile, repaglinide has been developed to specifically target meal-related insulin requirements in type 2 diabetes.

MATERIAL & METHODS

This randomized prospective study of one year duration (Sep. 2005-Sep.2006) was carried out in two hundred patients both male and female aging between 30-65 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:

Personal bio-data like age, sex, occupation, address and telephone numbers was recorded. In addition family history of diabetes mellitus and personal history was taken. Usual symptoms which had compelled the patients to seek advice (symptoms at presentation) were also inquired. They included polyuria, polydipsia, polyphagia, headache, dizziness, fatigue, lethargy, body ache and pains. Symptoms due to complications of diabetes mellitus like palpitation, chest pain, dyspnea, facial puffiness, transient ischaemic attack, burning sensation and numbness of extremities and blurred vision were also asked for. This was done to rule out undiagnosed long standing diabetes mellitus.

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

Investigations: Following investigations were carried out in all the patients at the start (day one) of the study. They included:

1. Fasting blood glucose
2. Two hours postprandial blood glucose

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)

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 Basic" glucose analyzer. Blood pressure was measured by using sphygmomanometer with appropriate cuff size. All of the results of the parameters (discussed above) were filled on a proforma specially designed for the study (attached at the end). Repaglinide was used as the only anti-diabetic drug in half of the subjects (termed as repaglinide group; N=100), stating with a low dose of 0.5mg three times a day, any time from 30 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 anti-diabetic drug in the other half (termed as glibenclamide group; n=100) 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 < 126mg/dl and postprandial blood glucose of < 160mg/dl. During the study period all the patients were treated with individualized weight maintaining diet (carbohydrates 55-60%, fat 30% and proteins 12-20%) with 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-style 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 laboratory test results. On every visit the patients were inquired about any side-effects of the drug he or she was taking. Symptoms of hypoglycemia (palpitations, nausea, sweating, dizziness, headache, etc.) were specifically 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 using SPSS software (version 17.0). Conclusions regarding safety and efficacy were drawn by comparing the results of the study patients with those of the control group. Students 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 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

Two hundred cases of newly diagnosed type 2 patients were studied. All of them were having age greater than 30 years to a maximum of 65 years. In the glibenclamide group, the mean age was 45.2 ± 8.2 years, while in the repaglinide group the mean age was 46.0±10.1 years.

Male to female ratio was different in both groups. In glibenclamide group (N=100), 20 were males (20%) and 80 were females (80%), while in the repaglinide group (N-100), 31 were males (31%) and 67 were females (67%). On the whole there were 27% males and 75% females in the study. The mean weight of glibenclamide group was 64.8±9.2 kilogram, while that of repaglinide group was 71.6±17. The mean height of the patients in glibenclamide group was 1.5±0.5m, while that of repaglinide group was 1.50±0.5. Body mass index (BMI) of glibenclamide and repaglinide groups was 30.2±5.5 and 27.2±3.2 respectively. In repaglinide group the mean dosage used was 4.27mg/day and in glibenclamide group it was 8.8mg/day.

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 weight. The mean values at the start, six months and at the end of one year of both the groups are given below.

Mean fasting blood glucose values of patients put on repaglinide at the start of the study was 161 ± 53, at six months 120±26 and at the end of one year, it was 105±11. In glibenclamide group, at the start it was 140 ± 50 at six months 110±18 and at the end of one year 103±12.7. Therefore, the mean reduction of fasting blood glucose level in repaglinide group was 63 ± 53 and glibenclamide 33.7± 52 (P = 0.006). 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 268± 73, 193±43 and 148±24 respectively, while that of glibenclamide group were 228.6±79, 176±40 and 140±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 118±66 and glibenclamide group was 88.6±74 (P=0.03).

The mean weight on the whole remained steady. There was a slight increase in the mean weight of repaglinide group and almost remained the same in glibenclamide group. The mean weight in repaglinide group at the start, six months and at one year was 66.8±9.5, 66±9.5, 65±8.7 respectively, while that of glibenclamide group was 72.5±17.3, 72.6±16.6 and 72.7±15.3 respectively. Therefore, the mean gain and reduction of weight in the whole study in repaglinide group was 0.3±4 and in glibenclamide group was 0.93±3.1. The P value was not significant.

DISCUSSION

The treatment of type 2 diabetic patients is ever changing. New therapies are emerging each year to provide convenience and benefit to the patients. One of the newer oral hypoglycaemic 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. Three major parameters were chosen to evaluate the drug. They were fasting blood glucose, two-hour postprandial blood glucose and weight. All these results were compared with a group of patients on glibenclamide, (which was to act as control) which is considered as a gold standard in the treatment of type 2 diabetic patients[13,14].

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=0.006). 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 - 118±66 and glibenclamide 88.0±74; P=0.03). These findings are consistent with the study by Landgraf which showed a decrease in fasting blood glucose and two hours postprandial blood glucose with a statistical significance[15].

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[16].

CONCLUSIONS

The conclusions drawn from our study are as follows:

- Repaglinide and glibenclamide were both well tolerated.
- They were both effective in lowering fasting blood glucose, two hours postprandial blood glucose and if used regularly for one year.
- 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. A larger study for a longer period of time is required to evaluate its importance in reducing the complications of diabetes.

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