The Role of Repaglinide in the Management of Type 2 Diabetes Mellitus

Abbas M Rahmah , Majid R Al-Zaidee , Roaa abbas

ABSTRACT:

BACKGROUND :

Repaglinide belongs to the meglitinide class of blood glucose-lowering drugs. Repaglinide lowers blood glucose by stimulating the release of insulin from the pancreas. It achieves this by closing ATP-dependent potassium channels in the membrane of the beta cells. This depolarizes the beta cells, opening the cells' calcium channels, and the resulting calcium influx induces insulin secretion.

OBJECTIVE:

To evaluate the effect of repaglinide as a monotherapy or in combination with metformin on controlling the fasting plasma glucose, postprandial plasma glucose, HBA1C, and body weight in 61 patients with type 2 diabetes mellitus, (DM).

PATEINTS & METHODS:

During the period between February 2005 and October 2005, the effects of repaglinide has been reviewed in 61 patients with uncontrolled Type 2 diabetes mellitus (T2DM), they are divided into two groups depending on their previous treatment , the 1st group included 43 of them were on metformin while the remaining 18 patients were on diet only. Weight, HBA1c, FPG and PPG were checked after 3 and 6 months.

RESULTS:

It has been found that six months after using Repaglinide in combination with metformin or as a monotherapy cause significant reduction in HBA1c, from 9.8 to 8.1% ($P < 0.01$) in 1st group, and from 7.9 to 6.7%, ($P < 0.01$) in 2nd group and a significant reduction of FPG from 214.0 mg/dl to 148.5 mg/dl ($P < 0.01$) in 1st group and from 170.7 mg/dl to 130 mg/dl ($P < 0.01$) in 2nd group**.** While the PPG shows a decrement from 255.6 mg/dl to 178.8 mg/dl, ($P < 0.01$) in 1st group and from 248.3 mg/dl to166.1 mg/dl ($P < 0.01$) in 2nd group. There's no significant weight gain thus mean weight rose from 84.4 Kg to 84.6 Kg, ($P > 0.2$) in 1st group and from 75.1 kg to 76.1 kg ($P > 0.2$) in 2nd group .

CONCLUSION:

Repaglinide when used as monotherapy or in combination with metformin improve overall glycemic control and significantly reduced HBA1c but have no significant change in body weight.

KEY WORDS: repaglinide, diabetes, control.

INTRODUCTION:

Normally meals are followed by a rapid increase in insulin secretion from pancreaticβ-cells. Plasma concentrations of insulin peak within 1 h after a meal and, as a consequence, blood glucose concentrations quickly revert to baseline levels. Postprandial glucose excursions are therefore small. However, in patients with type 2 diabetes, postprandial insulin secretion is impaired as a result of abnormal β-cell function. This leads to inadequate glucose disposal and hence to postprandial hyperglycaemia and loss of glycaemic control [(1)].

Postprandial hyperglycemia is a prominent and early defect in subjects with type 2 diabetes. The exaggerated mealtime blood glucose excursion characteristic of type 2

ALSadar Hospital National Diabetes Center
ALMustansyria University.

diabetes is due to inadequate suppression of endogenous glucose production caused by loss of early-phase insulin response [2]

Hyperglycaemia is a major factor in the development of long-term diabetic complications. Good control of mean blood glucose concentrations can prevent the development of microvascular complications[3] Evidence suggests that postprandial hyperglycaemia is also a risk factor for macrovascular disease, independently of fasting blood glucose concentrations[4]

Recent studies have shown that mealtime hyperglycemia may be a more accurate predictor of HbA1c levels [5] and of cardiovascular mortality [6,7] than fasting hyperglycemia. This information has focused attention on postmeal glycemic control. The ideal oral agent to target postprandial hyperglycemia should restore early phase insulin release without late hyperinsulinemia or an increased risk of hypoglycemia [8,9].

Repaglinide, a carbamoylmethyl benzoic acid derivative, is rapidly absorbed, metabolized by the liver and eliminated primarily via the bile. It has a short duration of action and is taken immediately before each main meal. This regimen has been shown to provide superior glycaemic control compared with regular morning and evening dosing. A flexible preprandial only dosing regimen of repaglinide significantly lowers the risk of hypoglycaemia if a meal is missed or postponed. Combination therapy with metformin improves glycaemic control significantly compared with therapy with either drug alone in overweight patients. Repaglinide has an equivalent safety and efficacy profile to the sulphonylureas, although it is superior to glipizide in maintaining long-term glycaemic control. The postprandial glucose levels are significantly lower with repaglinide compared with glibenclamide. In type 2 diabetic patients in whom dietary manipulation was the only modality of treatment , repaglinide lowers fasting glucose concentrations and functions also as a prandial glucose regulator [10].

PATIENTS& METHODS:

Sixty-one patients with poorly controlled type 2 diabetes attending the National center of Diabetes during period between February 2005 and October 2005 were enrolled in this study. The enrolled patients were divided into two groups depending on their treatment before study entry. The 1st group involved forty-three patients were on metformin while the 2nd group involved eighteen patients were on diet treatment only. The glycemic control in both groups were poor on the basis of high FPG, PPG, and HBA1c thus control doesn't fulfill the targets proposed by the European policy Data Group which are HBA1c less than 7%, FPG less than 128 mg/dl, and PPG less than 135 mg/dl.

Their control also does not fulfill the targets proposed by the American Diabetes Association, which are (HBA1c < 7 % and FPG < 131 mg/dl).

At study entry, the enrolled subject in 1st group had a mean HBA1c of (9.8%±1.6), mean FPG of(214mg/dl±59.0), mean PP±G of(255.7 mg/dl±77.1) and mean weight of (84.4 ±16.8). While patients in 2nd group had a mean HBA1c of(7.9%± 1.5), mean FPG of (170.7mg/dl±40.2), mean PPG of(248.4mg/dl±43.2) and mean weight of (75.1Kg ±10.4). At study entry, all patients in both groups are treated with Repaglinide in doses ranging from 0.5 mg to 2 mg before each main meal. Before starting this medication, the details of the study explained to the enrolled patients. They were informed about Repaglinide action, benefits, and expected side effects.

After full explanation, the patients accepted the idea and all patients were provided with an informed consent. At the first visit, the entire enrolled patient, full story was taken followed by physical examination including weight and blood samples taken to check FPG, PPG, and HBA1c. All these parameters are reevaluated at an interim visit 3 months later and final visit 6 months after enrollment.

STATISTICAL ANALYSIS

All data were coded and entered to computer by using Statistical Package For Social Science (SPSS 4) association

between variables measured by using Chi-square test. Difference between variables measured by using t-test, P< 0.05 considered as a level of significance.

RESULTS :

The enrolled diabetic patients were 61 patients (43 males & 18 females), their age ranges from 28 to 66 years with a mean age of(50.30 years± 8.2) .

Forty-three patients represent the 1st group who were treated with metformin , while the remaining 18 patients represent the 2nd group , their treatment was by dietary modification only

The glycosylated haemoglobin (HBA1c) on recruitment was(9.8 % ±1.6) for the 1st group and (7.9% ±1.5)for the 2nd group. The addition of repaglinide to their initial therapy result in decrement in HBA1c, in the 1st group from 9.8% to8.1% (-1.7%), and from 7.9% to 6.7% (-1.2%) in the 2nd group. The effect of repaglinide on HBA1c is statistically significant in both groups of patients (P< 0.01) as shown in figure 1.

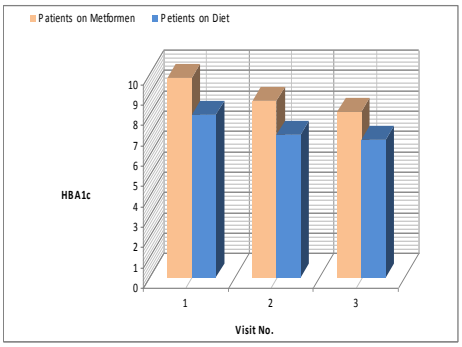

Figure 1: Changes in HBA1c before and after adding Repaglinide in both Groups.1 (HBA1c in both groups on enrollment), 2 (HBA1c in both groups at visit 2 after 3 months), 3 (HBA1c in both groups at visit 3 after 6 months)

Six months treatment with repaglinide shows significant improvement in glycemic control (FPG& PPG) in both groups, in 1st group the baseline FPG was 214 mg/dl changed to 148.5 mg/dl (-65.5 mg/dl) with P value < 0.01 while in 2nd group the FPG was reduced from 170.7 mg/dl to 130 mg/dl (-40.7) with P value <0.01 as shown in Figure 2. While changes in PPG shown in Figure 3, the PPG in 1st group drops from 255.7 mg/dl to 178.8 mg/dl (-76.9mg/dl) with P value < 0.01 and in 2nd group postprandial shows drops from 248.4 mg/dl to 166.1 mg/dl (-82.3 mg/dl) with P value <0.01.

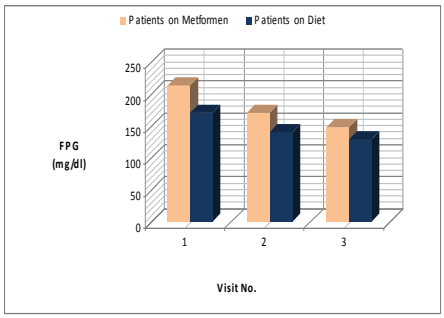

Figure 2: Reductions in FPG after adding Repaglinide. 1 (FPG in both groups on enrollment), 2 (FPG in both groups at visit 2 after 3 months), 3 (FPG in both groups at visit 3 after 6 months).

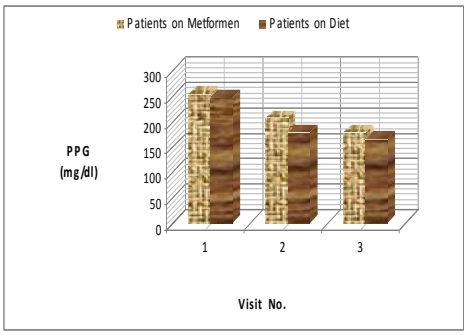

Figure 3: Reductions in PPG after adding Repaglinide. 1 (PPG in both groups on enrollment), 2 (PPG in both groups at visit 2 after 3 months), 3 (PPG in both groups at visit 3 after 6 months).

The addition of repaglinide results in a non-significant weight gain in both groups of diabetics patients thus body weight in 1st group rose from a mean of 84.4 kg to 84.6 kg (+ 0.2 kg) with P value > 0.2 while in the 2nd group it rose from 75.1 kg to 76.1 kg (+ 1 kg) after six months of using repaglinide ,such increase is found not to be statistically significant with P value > 0.2.as shown in figure 4

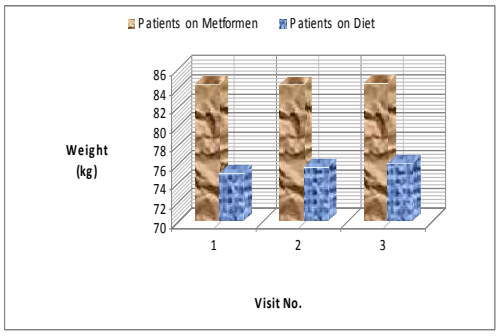

Figure 4: Increment in Body Weight in both Groups 1 (weight [kg] in both groups on enrollment), 2 (weight [kg] in both groups at visit 2 after 3 months), 3 (weight [kg] in both groups at visit 3 after 6 months).

DISCUSSION:

The value of good glycemic control in type 2 diabetes was shown beyond doubt by the United Kingdom Prospectve Diabetes Study (UKPDS) [3], which confirmed a number of previous studies in type 2 diabets [14,15].

While it improves overall glycemic control, repaglinide was developed specifically for dosing at mealtime, to control postprandial hyperglycemia. In this study was used repaglinide as monotherapy or in addition to metformin for individuals with type 2 diabetes whose hyperglycemia cannot be controlled by diet or metformin alone.

In the current study mealtime dosing of repaglinide clearly demonstrated a near-normalization of glycemic control and cause reductions not only in postprandial glucose, but also in fasting glucose and HbA1c levels and this reinforce the clinical experience with repaglinide as reported by other studies,

Our study shows that the use of repaglinide in treatment of type 2 DM cause significant reduction in HbA1c in both groups (P< 0.01 in both groups) as shown in Figure 1 and this is comparable with result of other studies [11,12,13], and this reduction in HbA1c proved that the repaglinide is useful drug for long term control of hyperglycemia.

Repaglinide as a monotherapy or in addition to metformen cause significant reductions in PPG, (P< 0.01 in both groups) as shown in Figure 3 ,these results are in harmony with the results of other studies [11,12,13], this alone is an important attribute of repaglinide because postprandial

hyperglycemia is increasingly suspected of involvement in the pathogenesis of late diabetic complications, especially cardiovascular morbidity. These changes also reflect the findings of Owens et al which proved that pre-prandial repaglinide induces insulin secetion 30 min after a solid meal and improved the early phase of insulin secretion in diabetic subjects. [6]

Repaglinide in both groups improves fasting (preprandial) glucose levels, ($P < 0.01$ in both groups) as shown in Figure 2 these findings match those in other studies with repaglinide [11,17]. These finding proved the fact that the reduction in prandial glucose excursions induced by this short-acting compound also leads to a reduction in fasting glycemia clearly underlines the importance of controlling prandial glycemia.

At the end of study, in comparison between both groups, in the 2nd group of patients who ar treated with diet modification befor adding repaglinide –the glycemic parameter (HBA1c 6.7% FPG 130 mg/dl ,PPG 166 mg/dl)were better than those in the 1st group in whom repaglinide added to metformin on recruitment . The tight glycemic control in the 2nd group may be attributed to the fact that, the patients of this group are more compliant and diatery modification is fretful to lower the glycemic parameters to a level at which the addition of repaglinide result decrement in these parameters down to the intended goals.

These improvements in glycemic parameter were achieved without a significant increase in body weight. Overall weight changes in this study were slight and insignificant, body weight remained relatively stable over time, mean body weight gain: 0.2kg in 1st group which is a insignificant change ($P > 0.2$) and 1 kg in 2nd group which a insignificant as well ($P > 0.2$) as shown in Figure 4. These findings match those found by other investigators [11]. The lack of weight gain in both groups is particularly encouraging, since improvement of glycemic control with other therapies is often associated with significant increases in weight, particularly with those therapies that increase total insulin exposure as in treatment with sulfonylureas [3], such induced weight gain is clinically undesirable in patients with type 2 diabetes.

CONCLUSION:

These data support a strategy of mealtime dosing with a rapid-acting insulin secretagogue such as repaglinide improve overall glycmic control without causing weight gain.

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