Efficacy & Safety of Repaglinide as Monotherapy or with Metformin in Achieving the Recommended Glycemic Targets of Type 2 Diabetes

MMJ 2008; 7:4-8

Tawfeeq F. R. Al-Auqbi*, Esam N. S. Al-Kirwi **
*F.I.C.M.S/C.M,** C.A.B.M (National Diabetes Center, Baghdad/Iraq)

Abstract:
Objectives: To assess the efficacy and safety of Repaglinide in achieving the recommended glycemic targets in type 2 diabetes.

Methods: Six months prospective interventional study (before and after treatment) was carried out on 125 type 2 diabetics treated by Repaglinide with/without metformin. Patients were interviewed three times, at the beginning, after three and six months each time they were examined physically and investigated thoroughly.

Results: Efficacy and safety parameters, fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycated hemoglobin (HbA1c) had shown a significant statistical reduction to meet the recommended glycemic control targets of the American Diabetes Association (ADA) and very close to the International Diabetes Federation, European Diabetes Policy Group (IDF) at the consecutive interviews. Lipid profiles values, Total cholesterol, LDL-C, HDL-C, non-HDL-C, triglyceride and atherogenic index (TC/ HDL-C ratio) were achieved significant statistical improvements.

Conclusions: Repaglinide as monotherapy or in combination with metformin was safe, efficacious and well tolerated for lowering plasma glucose in type 2 diabetes, achieving the internationally recommended glycemic targets and improving the lipid profile values.

Keywords: Type 2 diabetes mellitus, Repaglinide, recommended glycemic targets, lipid profile.

Introduction:
Diabetes is a prevalent multi-system metabolic disease associated with high health care resource expenditures\(^1\). The American Diabetes Association (ADA) estimated that in 1997, 10.2 million (5.1%) U.S. adults were newly diagnosed with diabetes, with another 5.4 million people (2.7%) unaware that they had the disease\(^2\). The costs of managing diabetes and its complications comprise 15% of total U.S. health care expenditures\(^3\). In 1997, direct medical health care expenditures for diabetes care were estimated to exceed $44.1 billion, with the majority of these costs related to inpatient care (62%), followed by outpatient services (25%) and nursing home care (13%)\(^4\). Nowadays, the cost of diabetes to the United States healthcare system is staggering, amounting to $100 billion in direct and indirect expenditures annually\(^5\).

Currently 15 million Americans have diabetes, one third of them have yet to be diagnosed. Ninety percent of these cases represent type 2 Diabetes Mellitus (T2DM). The incidence of type 2 DM and its precursor (impaired glucose tolerance) continues to rise, paralleling that of overweight and obesity\(^6\). Remarkably, this is occurring in children and adolescents, as well as adults\(^7\). The increased risk of cardiovascular disease (CVD) in type 2 DM has led to more stringent goals for the management of cholesterol and blood pressure, in addition to the use of aspirin\(^8\), and statin for diabetics. Therefore, close attention should be paid to the overall cardiovascular health of patients with type 2 DM, not just their glycated hemoglobin (HbA1c)\(^9\). Moreover, the macro
vascular and micro vascular complications associated with diabetes are well documented by the U.K. Prospective Diabetes Study (UKPDS)\(^{10}\), Diabetes Control and Complications Trial (DCCT) Research Group, the Third National Health and Nutrition Examination Survey, the American Diabetes Association (ADA) publications and other studies\(^{11-12}\).

The current management guidelines have suggested more aggressive goals for glycemic control\(^{12-13}\). The WHO criteria for diabetes include a fasting plasma glucose ≥7.0, or ≥11.1 2 h post 75 g oral glucose tolerance test (OGTT)\(^{14}\). Lesser degrees of abnormal glucose metabolism are classified as impaired fasting glycaemia (IFG) (fasting glucose ≥6.1 and <7.0) and impaired glucose tolerance (IGT) (plasma glucose ≥7.8 and <11.1 2 h following a 75 g OGTT), and are also associated with increased cardiovascular risk\(^{15-16}\). Treatment of abnormal glucose metabolism is initially with non-pharmacological measures, including diet, exercise and weight loss, as well as, other cardiovascular risk factors such as smoking, hypertension, microalbuminuria, and dyslipidaemia should be addressed\(^{17}\). Unfortunately these lifestyle measures are often unsuccessful, and pharmacological therapy is required to improve glycemic control\(^{10,18}\).

In the past two decades there has been a significant increase in the number of drugs available to treat the hyperglycaemia of type 2 diabetes, and five different types of oral antidiabetic agents (OAD) are currently available\(^{19}\). Repaglinide (Novo Norm, Prandin) is an insulin secretagogue with a rapid onset and relatively short duration of action\(^{20-21}\), elimination half-life was about 1 hour\(^{22}\).

It is approved for the treatment of type 2 diabetes\(^{23-24}\), when administered at mealtimes it produce peak insulin stimulation during the postprandial period, when the physiological insulin needs are maximal. Clinical trials have demonstrated that increase insulin response to postprandial glucose, resulting in reductions of HbA1c and fasting plasma glucose (FPG) levels\(^{22}\).

This study had been designed to assess the efficacy and safety of Repaglinide as monotherapy or with metformin in achieving the recommended glycemic targets in type 2 diabetes.

**Patients & Methods:**

Six months period (Nov. 2004 – Apr. 2005) prospective study, before and after intervention, for the use of Repaglinide as monotherapy or in combination with metformin was carried out on one hundred and twenty five type 2 diabetics who were registered in the National Diabetes Center (NDC) / Al-Mustansiriya University, after obtaining their agreements according to the medical research and ethical regulations, thus an oral consent was taken from all enrolled participants.

Patients selected to participate in the study, 56 female and 69 male (F/M ratio =1/1.23), had mean ±SD of age 55.9 ± 8.5 years, diabetes duration 7.9 ± 5.1 years, BMI 29.57 ± 5.1 kg/m2, HbA1c 8.95 ± 1.55 %. All patients were interviewed three times, at the beginning, after three months and after six months at the end of the study; each time participants were asked about any associated disease, side effect, complications, coexistent treatment, adverse events, hypoglycemic events and examined physically (height, weight); then fasting and postprandial blood sampels were taken for laboratory investigations. The efficacy variables including fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), glycated hemoglobin (HbA1c); as well as, the safety variables included plasma lipids [serum total cholesterol (TC), serum triglycerides, LDL-C, VLDL-C, non HDL-C, HDL-C and atherogenic index (TC/HDL ratio)], BMI, adverse effects and hypoglycemia. [25]

Repaglinide (Novo Norm®) was used in the study as 1, 2 and 3 mg tablets taken three times before meals (pre prandial dose). Metformin (glucophage)was used as 500 mg tablets three times after meal (post prandial dose).

Statistical analysis and reporting of obtained data were carried out by using Microsoft Excel - Windows XP professional program. Statistical tests were performed using a null hypothesis of no difference with a two-tails paired student t-test; the level of significane of P value was ≤ 0.05 and of high significance was ≤0.01.
Results:
A total of one hundred and twenty five type 2 diabetic patients had been complete the six months trial without withdrawal problems.

The efficacy parameters of glycemic control, (FPG), (PPG) and (HbA1c) were found at the baseline investigations 181.3±43.5 mg/dl, 290.5±85.7 mg/dl and 8.95±1.55% respectively; after three months, parameters shown a significant statistical reduction and found as 149.1±28.1 mg/dl, 209.1±44.7 mg/dl and 7.80±1.39 % respectively (table 1). After six months (FPG), (PPG) and (HbA1c) persisting to show the same pattern of a significant statistical reduction and found as 122.7±18.6 mg/dl, 173.4±25.4 mg/dl and 6.83±0.89 % respectively, to the limit reaching the recommended glycemic control targets of the American Diabetes Association (ADA) and very close to the International Diabetes Federation, European Diabetes Policy Group (IDF) stringent recommendations (table 1).

The efficacy parameters of glycemic control (FPG), (PPG) and (HbA1c) reduced gradually during the period of study, the percent of reduction or achievements after three months were found to be 17.7%, 28.0% and 12.8% respectively; and after six months the percents were 32.3%, 40.3% and 23.8% respectively (table 2).

The safety parameters of glycemic control, lipid profile, were measured at the beginning and after three months of the study. The triglycerides, HDL-c, VLDL-c, non-HDL-c and attherogenic index (total cholesterol/HDL-c ratio) were achieving high statistical significant difference of improvement percents (P-value <0.01) as 27.04%, -12.25%, 24.03%, 23.0% and 10.7% respectively; the total cholesterol and LDL-c was achieving significant statistical improvement percents (P-value <0.05) as 17.6% and 24.3% respectively. After three months of treatment the National Cholesterol Education Program (NCEP)/Adult Treatment Panel III (ATP III) guidelines recommended targets [26] were achieved (table 3).

Ninty four patients, 75.2% of participants, required metformin 1500 mg/day in three divided doses to be added to their course of treatment to achieve the recommended glycemic targets. Two patients experienced bouts of mild hypoglycemia during the course of the study which were managed by the patients themselves without further complication.

Patients were showed mild reduction in their BMI mean at the consecutive appraisals, baseline, after three and six months, as 29.57±5.13, 29.50±5.00 and 29.35±4.95 kg/m2 respectively.

Table-1: The glycemic control parameters, fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycated hemoglobin (HbA1c) and the recommended glycemic targets.

<table>
<thead>
<tr>
<th>Findings</th>
<th>Baseline</th>
<th>After 3 months</th>
<th>After 6 months</th>
<th>IDF *</th>
<th>ADA **</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG mmol/l</td>
<td>9.99±2.39</td>
<td>8.21±1.54</td>
<td>6.76±1.02</td>
<td>≤ 5.5</td>
<td>5.0 – 7.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>FPG mg/dl</td>
<td>181.3±43.5</td>
<td>149.1±28.1</td>
<td>122.7±18.6</td>
<td>≤ 99</td>
<td>90 - 130</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PPG mmol/l</td>
<td>16.0±4.72</td>
<td>11.5±2.4</td>
<td>9.5±1.4</td>
<td>&lt; 7.5</td>
<td>5.0 – 7.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PPG mg/dl</td>
<td>290.5±85.7</td>
<td>209.1±44.7</td>
<td>173.4±25.4</td>
<td>&lt; 135</td>
<td>90 - 130</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.95±1.55</td>
<td>7.80±1.39</td>
<td>6.83±0.89</td>
<td>≤ 6.5</td>
<td>5.0 – 7.2</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

* International Diabetes Federation, European Diabetes Policy Group [27].
** American Diabetes Association [12].
Table-2: Amount and percent of achievement in the efficacy glycemic control parameters fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycated hemoglobin (HbA1c) after three and six months.

<table>
<thead>
<tr>
<th>Achievements</th>
<th>After 3 months</th>
<th>After 6 months</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/l</td>
<td>8.21±1.54</td>
<td>6.76±1.02</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>mg/dl</td>
<td>149.1±28.1</td>
<td>122.7±18.6</td>
<td></td>
</tr>
<tr>
<td>% of reduction</td>
<td>17.74</td>
<td>32.30</td>
<td></td>
</tr>
<tr>
<td>PPG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmol/l</td>
<td>11.5±2.4</td>
<td>9.5±1.4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>mg/dl</td>
<td>209.1±44.7</td>
<td>173.4±25.4</td>
<td></td>
</tr>
<tr>
<td>% of reduction</td>
<td>28.03</td>
<td>40.30</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>7.80±1.39</td>
<td>6.83±0.89</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>% of reduction</td>
<td>12.8</td>
<td>23.8</td>
<td></td>
</tr>
</tbody>
</table>

Table-3: Baseline and after three months findings of lipid profile values, percent of reduction, and the recommended glycemic targets.

<table>
<thead>
<tr>
<th>Findings (mean±SD)</th>
<th>Baseline</th>
<th>After 3 months</th>
<th>% improvement</th>
<th>NCEP *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mg/dl)</td>
<td>204.8±41.4</td>
<td>171.7±32.5</td>
<td>17.6 % ††</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>207.4±95.7</td>
<td>151.3±64.3</td>
<td>27.04% †</td>
<td>&lt;150</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>127.5±32.9</td>
<td>96.5±19.9</td>
<td>24.3% ††</td>
<td>&lt;100</td>
</tr>
<tr>
<td>VLDL-C (mg/dl)</td>
<td>36.2±17.7</td>
<td>27.5±9.7</td>
<td>24.03% †</td>
<td>&lt;30</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>40.0±9.9</td>
<td>44.9±8.7</td>
<td>-12.25% †</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Non HDL-C (mg/dl)</td>
<td>164.7±42.3</td>
<td>126.7±33.9</td>
<td>23.0% †</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Atherogenic index</td>
<td>4.47±2.01</td>
<td>3.99±1.24</td>
<td>10.7% †</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

* National Cholesterol Education Program/Adult Treatment Panel III (ATP III) Guidelines. [26]
† = P-value <0.01, †† = P-value <0.05

Discussion:
The International Diabetes Federation (IDF) at 1999 intentionally undertakes the targets published by the European Diabetes Policy Group for the stringent type 2 diabetes glycemic control and considered as recommended targets, HbA1C ≤ 6.5%(27); However, an HbA1C < 7.0% is only achieved in 36% of diabetic patients(13). Later on, 2004, the American Diabetes Association (ADA) undertakes lesser tight recommendations as recommended targets, as an HbA1C ≤ 7.0%, for good glycemic control(12). Our data obtained after, three and six months (table 1, 2) shown clearly how patients had achieved the recommended glycemic targets, percentages of achievements reach up to 40.3% after three months, by using Repaglinide as monotherapy or in combination with metformin in spite of the educational, cultural, economical and technical obstacles.

Several landmark studies clearly document that patients who aggressively control their blood glucose levels are less likely to develop complications associated with diabetes(10,28). In addition, Emerging data from the Epidemiology of Diabetes Interventions and Complications (EDIC) study, and the long-term follow-up of the Diabetes Control and Complications Trial (DCCT), also support the benefits of glycemic control for cardiovascular risk reduction(19-20). With respect to reaching goals of these studies, the guidelines emphasize lifestyle modifications, regarding diet, exercise, patient education and regular follow-up to prevent or delay complications(29).

The Framingham Heart Study, [30] the Multiple Risk Factor Intervention Trial (MRFIT)(30), and the Lipid Research Clinics (LRC) trial(32-33) found a direct relationship between levels of LDL cholesterol
or total cholesterol and the rate of new-onset of CHD in men and women who were initially free of CHD. Results obtained from present study showed, after three months of intervention, statistically significant reduction in the lipid profile values and elevation of HDL-cholesterol; all the changes in mean of lipid profile values were toward the international recommended targets (table-3). Though Ronald et.al. found that mean of total cholesterol, HDL-C, LDL-C and triglyceride were not significantly elevated or there were no significant differences between groups treated by Repaglinide and other modality of treatment or placebo^{25}; but the present study clearly manifest the statistically significant differences between mean of total cholesterol, HDL-C, LDL-C and triglyceride before and after treatment by Repaglinide with/without Metformin. Peter Damsbo et.al. findings were supporting finding of the present study^{34}, who proved the significant reduction of serum cholesterol and triglyceride for patients treated by Repaglinide and they attribute these significant alterations to the weight loss occurred during their trail, the same things were noticed during our study.

Hypoglycemia was noticed in up to 20% of patients as an adverse effect for the treatment by sulphonylurea^{35}; While, two patients, 1.6% of participants, during present study suffering from an attack of hypoglycemia, this, might be, because the incidence of hypoglycemia appears to be greater with long acting agents than with short acting OADs^{36}. So the American Diabetes Association (ADA) and the European type 2 policy group recommend using of short acting OADs drugs since 1980s^{37-38}. Only thirty one patients, 24.8% of the participants, achieved the glycemic targets by using repaglinide as monotherapy; and ninety four patients, 75.2% of participants, required metformin 1500 mg/day in three divided doses to be added to their course of treatment to achieve the recommended glycemic targets. Moses et.al. elucidate that combined metformin and repaglinide therapy resulted in superior glycemic control compared with repaglinide or metformin monotherapy in patients with type 2 diabetes whose glycemia had not been well controlled. Repaglinide monotherapy was as effective as metformin monotherapy^{39}.

**Conclusion:**
The present study demonstrated that Repaglinide as monotherapy or with metformin was safe, efficacious and well tolerated for lowering plasma glucose in type 2 diabetes, achieving the internationally recommended glycemic targets and improving the lipid profile values.

**References:**
15. The DECODE Study Group, on behalf of the European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and non cardiovascular diseases? Diabetes Care 2003; 26: 688–696.