Comparative Effects of Repaglinide Versus Glibenclamide on Glycemic Control in Newly Diagnosed Type 2 Diabetic Patients

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Abstract

Repaglinide is an oral prandial glucose regulator indicated for treatment of type 2 diabetic patients through its mechanism in improving first phase insulin secretion which can lower postprandial plasma glucose. To compare the effects of repaglinide versus glibenclamide on glycemic control in newly diagnosed type 2 diabetic patients. Twenty-four recently diagnosed diabetic patients were enrolled in this non-randomized clinical trial. They were classified into two groups, 12 patients received repaglinide and 12 patients received glibenclamide. Fasting plasma glucose (FPG), 2hour postprandial plasma glucose (2h. PPG) and glycated hemoglobin (HbA1c) were measured at the baseline and after 8 weeks follow up. Repaglinide decreased 2h. PPG significantly more than glibenclamide after 8 weeks without significant differences in reducing FPG and HbA1c between both treatment groups after 8 weeks. Repaglinide can be considered as an ideal agent in controlling postprandial hyperglycemia as a monotherapy or in combination with other oral hypoglycemic agents. Repaglinide, glibenclamide, postprandial hyperglycemia.

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الملخص

يعتبر عقار االرابيكلينايد احد منظمات مستوى السكر في الدم بعد الطعام في المرضى المصابين بداء السكر نوع 2 من خلال زيادة إفراز المستوى الاول من الانسولين والذي بدوره يؤدي الى انخفاض ملح وظ في مستوى السكر بعد ألطعام . مقارنة تأثيرات عقار الريبكلينايد والكليبنيكلامايد على السيطرة السكرية في المرضى المصابين بداء السكر نوع 2 والمشخصين حديثا. شملت ألدراسة 24 مريضا من المصابين بداء السكر نوع 2 وألمشخصين حديثا شاركوا في الدراسة الحالية (دراسة سريرية لا عشوائية). تم تقسيمهم الى مجموعتين، شملت كل مجموعة على 12 مريض، اعطيت المجموعة الاولى عقار الريبكلينايد بجرعة 2ملغم ثلاث مرات يوميا واعطيت المجموعة الثانية عقار الكليبنيكلامايد بجرعة 5 ملغم مرة واحدة يوميا . تمت متابعة المرضى لمدة 8 أسابيع، ثم تمت مقارنة مستويات السكر في الدم بعد الطعام وبعد الصيام وخضاب الدم المسكر قبل وبعد العلاج . اشارت الدراسة الحالية الى وجود انخفاض ملحوظ في مستوى السكر بعد الطعام في المرضى المعالجين بعقار الريبكلينايد بعد 8 أسابيع من العلاج مقارنة بمستوى السكر بعد الطعام للمرض ى المعالجين بعقار الكليبنيكلامايد في حين لم يلاحظ اي فروقات معنوية بين المجموعتين في مستوى السكر بعد الصيام و خضاب الدم المسكر.يعتبر عقار االرابيكلينايد-من خلال سيطرته على مستوى السكر بعد الطعام- عقار مثالي وواعد للوصول الى السيطرة السكرية المثالية كعلاج احادي او ثنائي.

Introduction

Type-2 diabetes mellitus (T2DM) is a heterogeneous disorder characterized by two interrelated metabolic defects: insulin resistance coupled with impaired insulin secretion by β-cells in the pancreas [(1)]. It's a multifactorial disease in which environmental factors appear to interact with multiple genetic variants in modulating the predisposition to the disease [(2)]. Fasting plasma glucose (FPG) is the plasma glucose level measured after an extended period (8-12 hours) with no caloric intake [(3)]. FPG levels ≥ 126mg/dl (7mmol/L) on two separate occasions constitute a diagnosis of diabetes (4). It is the measure preferred by the American Diabetes Association (ADA) for the diagnosis of diabetes because of its ease, relatively low cost, and extensive standardization [(3)]. Postprandial plasma glucose (PPG) is the plasma glucose level measured 2-hour after eating [(5)]. A plasma glucose level ≥ 200mg/dl (11.1mmol/L) 2h. after meal is diagnostic of diabetes [(4)]. Although the use of FPG is simpler and more reproducible, the omission of the 2-h. PG will miss a proportion of diabetic subjects who have normal FPG but elevated 2-h. PG levels [(6)]. Recent studies have shown that mealtime hyperglycemia may be a more accurate predictor of HbA1c levels and of cardiovascular mortality than fasting hyperglycemia [(7)]. Glycated hemoglobin (HbA1c) expressed, as the percentage of adult hemoglobin that is glycated, is the most widely used measure of chronic glycemia[(8)]. HbA1c is the gold standard for assessing glucose homeostasis and it is an integration of both fasting and postprandial glucose variations over a 2-3 months period [(9)]. Repaglinide is a novel, fast acting, oral prandial glucose regulator indicated for the treatment of T2DM. It is the first member of the carbamoylmethy benzoic acid chemical family to be used in a clinical setting representing a new chemical class of insulin secretagogues [(10)]. It was approved by FDA in 1997 and it's developed for use as a prandial glucose regulator in a flexible mealtime dosing schedule ('one meal, one dose, no meal, no dose') [(11)]. Repaglinide increases the amount of insulin released in a natural and physiological pulsatile pattern and is not effective in the absence of functioning β–cells [(12)]. Thus, repaglinide is the first insulin secretagogue developed to target postprandial hyperglycemia and its rapid onset of action and short-lived hypoglycemic effect, makes it an ideal agent for controlling postprandial hyperglycemia [(13, 14)]. The aim of the present work is to compare the effects of repaglinide and glibenclamide on glycemic control in newly diagnosed type 2 diabetic patients at the baseline and after 8 weeks follow-up of repaglinide monotherapy.

Patients and methods

This study was carried out with ethical and scientific approval of the regional research committee of Mosul health administration, and was conducted at Al-Wafaa Center of Diabetes Management and Research in Mosul during the period from 1st of December 2010 to 10th of April 2011. Non-randomized clinical trial follow-up study design was adopted to achieve the aims of the current study. Twenty-four diabetic patients were enrolled in this study classified into 2 groups:

1. Group (1), included twelve newly diagnosed diabetic patients received repaglinide (Novo Norm) [Novo Nordisk, Denmark] monotherapy (2mg t.i.d. before each meal).
2. Group (2), included twelve newly diagnosed diabetic patients received Glibenclamide (Glibesyn)

[Medochemie, Cyprus] monotherapy (5mg once daily).

Informed consent was obtained from all patients participate in the study and approval to use the drug and to re-evaluate them after 8 weeks. 4 ml of venous blood have been collected after 8h. overnight fasting. 2ml of blood was transferred into fluoride test tube containing sodium fluoride to inhibit glycolysis, allowed to stand then separated by centrifugation at 3000 rpm. for 10 min., the resultant plasma was used for measurement of glucose. For HbA1c measurement, 2ml of blood was transferred into EDTA test tube, to obtain whole blood sample that was used for HbA1c measurement. For measurement of postprandial glucose concentration, patients were allowed to take breakfast following collection of fasting blood samples (group 1 patients given repaglinide tablet (2 mg) and instructed to take breakfast after 15 min., similarly, group 2 patients received glibenclamide tablet (5 mg) before taking breakfast) and after 2hr. 2ml of venous blood were collected and transferred into fluoride test tube for measurement of postprandial glucose concentrations. Plasma glucose was measured by oxidase-peroxidase method[15] which is highly specific for D-glucose, using a kit supplied from Randox (U.K.). HbA1c was measured in whole blood sample by ion-exchange resin quantitative colorimetric determination [16], using a kit supplied from Stanbio (USA).

Statistical analysis

paired t-test was used to compare the results of various biochemical parameters between the diabetic patients before and after therapy. Analysis of Variance (ANOVA) and Duncan multiple range test were used to compare the results of various biochemical parameters between different groups. P-value ≤ 0.05 was considered to be statistically significant.

Results

Table (1): Demographic and clinical characteristics of the studied groups

Characteristics		Group 1		Group 2	
		No.	%	No.	%
Age (years)	< 40	-	-	3	25
	41- 50	5	41.7	2	16.7
	51-60	4	33.3	4	33.3
	≥60	3	25	3	25
Gender	Male	8	66.7	7	58.3
	Female	4	33.3	5	41.7
	Total	12	100	12	100
Family History	Present	7	58.3	8	66.7
	Absent	5	41.7	4	33.3
Duration of DM (years)	< 1	10	83.3	9	75
	1-5	2	16.7	3	25
BMI	< 25	4	33.3	3	25
	≥ 25	8	66.7	9	75

Table (2): Effects of repaglinide and glibenclamide on FPG, 2h. PPG and HbA1c in newly diagnosed patients

Parameter	Period	Repaglinide	P-value	Glibenclamide	P-value
FPG (mg/dl)	At baseline	271.0 ± 61.32	< 0.001	169.95 ± 77.53	**NS**
	After 8weeks	145.8 ± 55.76		163.65 ± 46.68	
2h. PPG (mg/dl)	At baseline	327.4 ± 88.39	< 0.001	267.6 ± 114.86	**NS**
	After 8weeks	175.0 ± 39.33		240.6 ± 88.62	
HbA1c%	At baseline	9.10 ± 1.54	< 0.001	8.64 ± 1.95	**NS**
	After 8weeks	7.50 ± 1.19		7.75 ± 1.84	

*Significant at *P*-value ≤ 0.05 using paired t-test

By comparing the values of FPG, 2h. PPG and HbA1c in newly diagnosed patients with T2DM before and after therapy, there was a highly significant ($p<0.001$) decrease in FPG, 2h. PPG and HbA1c after 8 weeks use of repaglinide, while no significant decrease in FPG, 2h.PPG and HbA1c noted in T2DM patients treated with glibenclamide after 8 weeks of treatment.

Table (3): Comparative effects of repaglinide versus glibenclamide on glycemic control after 8 weeks

Parameters		Repaglinide	Glibenclamide
FPG (mg/dl)	At baseline	217 ± 61.3 (a)	169.9 ± 77.5 (a)
	After 8 week	145.8 ± 55.7 (a)	163.6 ± 46.6 (a)
PPG (mg/dl)	At baseline	327.4 ± 88.3 (a)	267.6 ± 114.8 (a)
	After 8 week	175 ± 39.3 (a)	240.6 ± 88.6 (b)
HbA1c %	At baseline	9.10 ± 1.5 (a)	8.64 ± 1.9 (a)
	After 8 week	7.72 ± 1.1 (a)	7.75 ± 1.8 (a)

Different litters horizontally indicate significant difference.

By comparing the results of FPG, 2h. PPG and HbA1c between the studied groups after 8 weeks follow up period; there was no significant difference in FPG and HbA1c between the two groups and a significant difference in 2h. PPG was observed between patients on repaglinide therapy after completing the follow up period against patients on glibenclamide treatment.

Discussion

The present study showed that both repaglinide and glibenclamide lowered FPG to a similar degree without significant difference between the both groups. These results were in

agreement with those reported by Manzella *et al.* [17], Abbatecola *et al.* [18] and Yngen *et al.* [19]. While Esposito *et al.* [20] found that glibenclamide lowered FPG more than repaglinide. In contrast, Papa *et al* [21] stated that repaglinide lower FPG significantly more than glibenclamide. As repaglinide is absorbed faster and has a shorter plasma half-life than glibenclamide, the morning FPG level in patients who received repaglinide was expected to be slightly higher than in those who received glibenclamide, owing to the long period since last dose. In fact, FPG did not differ significantly between the two treatment groups. Regarding postprandial hyperglycemia, the present study revealed that patients treated with repaglinide had a lower mean 2h. PPG level than patients who had received glibenclamide with significant difference between the two groups at the end of this trail. This was in agreement with Cozma *et al* [22] whose study showed that repaglinide maintained their efficacy on decreasing the postprandial glucose peaks in T2DM patients but glibenclamide does not significantly impact the peak postprandial glucose, similarly, this finding was consistent with other studies [23, 24, 25, 17]. This result may be explained by the rapid absorption of repaglinide which ensures maximum effects during meal-related glucose absorption. In diabetes, the postprandial phase is characterized by a rapid and large increase in blood glucose levels, and the possibility that these postprandial "hyperglycemic spikes" may be relevant to the pathophysiology of late diabetes complications, in particular cardiovascular complications (26). Therefore, treatment with repaglinide, in the long term, may reduce the risk of both micro and macrovascular complications in diabetic patients [27]. Long glycemic control, assessed by HbA1c, was found to be clinically equivalent in the repaglinide and glibenclamide groups, with no significant difference between the two treatment groups at the end of the study. In the repaglinide group, the mean HbA1c value decreased from 9.10% at the baseline to 7.50% at the end of the study, compared with a decrease from 8.64% to 7.75% in the glibenclamide group. This result was differing from that reported by Papa *et al* [21] who stated that repaglinide decreases HbA1c significantly more than glibenclamide in elderly type 2 diabetic patients following 24 weeks of treatment and in the 16-week study Moses *et al* [28] found that repaglinide produced significant decreases in HbA1c in type 2 diabetic patients. This difference between these studies and the present study could be attributed to the long duration of follow up and large sample size in the above two studies. The present study conclude that repaglinide is an insulin secretagogue developed to target postprandial hyperglycemia and its rapid onset of action and short-lived hypoglycemic effect, makes it an ideal agent for controlling postprandial hyperglycemia, thus it is a promising new drug in the treatment of T2DM, as a monotherapy or in combination with other hypoglycemic agents.

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