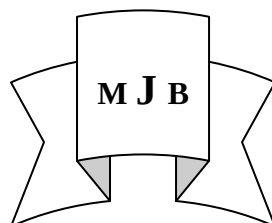


The Role of Repaglinide in the Treatment of Secondary Sulphonylureas Failure

Safaa Ali Khudhair

College of Medicine / Kufa University, Iraq.



Abstract

Background: About [20%-25%] of type 2 diabetes patients are unresponsive to sulphonylureas (primary failure) and an additional 5%-10% of patients each year become unresponsive (secondary failure).

Objective: Assessment of the efficacy of repaglinide in the treatment of secondary sulphonylurea failure.

Patients and Method: 48 patients with type 2 DM who failed to respond to a combination of full dose of glibenclamide and metformin are put on combination of repaglinide (3mg/day) and metformin and blood glucose is monitored for 9-11 weeks.

Results: 12 patients [25%] out of 48 patients with secondary sulphonylureas failure obtained good glycemic control with repaglinide.

Conclusion: Repaglinide can induce good glycemic control in some patients with secondary sulphonylureas failure.

فعالية عقار الريباكلازيد في علاج حالات فشل عقار السلفونيل يوريا

الخلاصة

تهدف هذه الدراسة الى قياس فعالية عقار الريباكلازيد في علاج مرضى داء السكري (النوع الثاني) من الذين فشلوا في الاستجابة لعقار السلفونيل يوريا.

شملت الدراسة على مرضى بداء السكري من النوع الثاني من الذين فشلوا في الاستجابة لعقار السلفونيل يوريا و عقار الميتفورمين معا . و قد تم اخضاع ٤٨ مريضاً لعقار الريباكلازيد بجرعة ٣ ملغم في اليوم مع عقار الميتفورمين في حين اخضع ٢٥ مريضاً للعلاج بالانسولين. اظهرت النتائج ان ١٢ مريضاً (٢٥%) استجابوا بشكل جيد لعقار الريباكلازيد في حين استجاب خمسة مرضى (٢٠%) بشكل جيد للعلاج بالانسولين و كان الفارق بين القيمتين ذو دلالة معنوية

Introduction

Diabetes mellitus is a chronic disorder characterized by the impaired metabolism of glucose and other energy-yielding fuels as well as by the late development of vascular and neuropathic complications[1].

Diagnostic criteria for diabetes mellitus recommended by WHO are [fasting plasma glucose $\geq$ 7mmol/l (126mg/dl) or random plasma glucose $\geq$ 11mmol/l (200mg/dl)]. These values are based on the threshold for risk of developing microvascular disease particular diabetic retinopathy. Less severe hyperglycemia is called

'impaired glucose tolerance'. This is not associated with substantial risk of microvascular disease, but is associated with increased risk of large vessel disease (e.g. atheroma leading to myocardial infarction) and with a greater risk of developing diabetes in future. The implication of these criteria is that there is no such thing as 'mild' diabetes not requiring effective treatment[2].

Diabetes mellitus is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy. The two broad

categories of DM are designated into type 1 and type 2. Type 2 DM is characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Type 2 diabetes accounts for the majority of diabetes encountered in clinical practice[3].

The clinical features of type 2 diabetes can be insidious; classic symptoms may be mild and may be tolerated for many years before the patient seeks medical attention. Moreover, if the degree of hyperglycemia is insufficient to produce any symptoms at all, the diagnosis can be made only after the development of vascular or neuropathic complications[4].

In some patients with type 2 diabetes mellitus, blood glucose control may initially be achieved with appropriate bodyweight reduction, diet and exercise. But, most patients eventually require drug therapy to maintain adequate glycaemic control. Various oral hypoglycemic agents have been developed over the past 40 years. These include sulphonylureas, biguanides, glucosidase inhibitors and thiazolidinediones. These drugs act through different mechanisms of action and can be used as monotherapy or in various combinations [5].

About 20%-25% of type 2 diabetes patients are unresponsive to sulphonylureas (primary failure) and an additional 5%-10% of patients each year become unresponsive (secondary failure) [6].

Repaglinide, arbamoylmethyl benzoic acid derivative and nateglinide, a dphenylalanine derivative, belong to a new class of oral hypoglycemic agents known as the meglitinide analogues. This class was developed to specifically control meal-related (prandial) glucose fluctuations in patients with type 2 diabetes mellitus [7].

Like the sulphonylureas, repaglinide acts by stimulating the release of insulin from the beta-cells of

the islets of pancreas inhibiting ATP-sensitive K^+ channels, thereby activating the Ca^{2+} channels with an increase in intracellular calcium to release insulin. However, repaglinide acts on a different binding site than the sulphonylureas[8, 9].

Repaglinide is a somewhat stronger secretagogue than nateglinide and similar to the sulphonylureas in glucose-lowering power, with an expected average HbA1c improvement of 1 to 2 % [10].

The rapid onset of action and the short duration of hypoglycemic effect of repaglinide makes this agent suitable for preprandial administration. The main advantage of preprandial administration is that patients can miss or postpone a meal (and the corresponding repaglinide dose) without increasing the risk of hypoglycemia or compromising glycaemic control [7].

The primary disadvantages of the meglitinides are their high cost and multiple dosing schedules and the lack of long-term outcomes data with these agents [10].

The activity of repaglinide is dose-dependent. Mean insulin levels begin to rise approximately 1.5 hours after the preprandial dose of repaglinide and declines towards baseline levels between meal time [11].

Repaglinide is rapidly absorbed after oral administration. Peak concentration occurs within 1 hr. of a single oral dose of 2mg. The mean oral bioavailability of repaglinide ranges from 56 to 63%.

Plasma concentrations of repaglinide fall rapidly, reaching predose concentrations within 4 or 5 hours after oral administration of 2 mg repaglinide[12].

Repaglinide is metabolized in the liver to inactive metabolites through the CYP3A4 enzyme system. Repaglinide and its metabolites are eliminated via the biliary-faecal route. Mild to moderate renal impairment (creatinine clearance > 30 ml/min) and

advanced age has little influence on the pharmacokinetics of repaglinide. However, individuals with severe renal impairment (creatinine clearance < 30 ml/min) or chronic liver disease, have higher and more prolonged serum levels of repaglinide than those in healthy individuals [13].

The repaglinide starting dosage is 0.5mg preprandially. However, if patients are transferred from another oral hypoglycemic drug or if HbA1c >8%, the starting dose should be higher (1-2mg.). Repaglinide can be given 15min. before a meal. If the patient misses a meal or adds a meal, he should omit or add the accompanying repaglinide dose. The recommended maximum dose is 16mg/day [7].

Aim of Study

To assess the efficacy of repaglinide in treatment of secondary sulphonylureas failure.

Patients and Methods

This study is conducted on 48 type 2 diabetic patients who attended Diabetic Clinic in Al- Hakim Center for Treatment and Researches of DM in Al-Sader Teaching Hospital in Al-Najaf over nine months period starting in February 2008.

All patients had diagnosed type 2 DM of 8.8 ± 5 years duration and were well controlled. But they had poor control in previous few months (mean fasting plasma glucose 266 ± 50 mg/dl) in spite of combined therapy of glibenclamide 10-15 mg /day and metformin 1500-2000 mg/day, which means they had secondary sulphonylureas failure.

Those patients are put on repaglinide (Novo Norm) tablet 3 mg/day in three divided dose before meal and combined with the same previous dose of metformin with meal; fasting plasma glucose (FPG) is

measured every 2-3 weeks for period of 10 ± 2 weeks.

Diabetic control was considered good if the mean FPG over a period of two months were less than 140 and poor if above this range. HbA1c was measured for some patients but not to all because of irregular availability of the test that why it is omitted from study.

The repaglinide group of the patients is compared with age and sex matched group of patients who had the same criteria of secondary sulphonylureas failure but they were treated with insulin.

Also we did study other parameters which may affect the response of the patients to repaglinide like age, sex, BMI, and duration of DM.

Statistical Study

The statistical analyses were based on Chi – square and t – tests with a p – value of 0.05 or less was considered statistically significant.

Results

The repaglinide group include 48 type 2 diabetic patients aged 40-58 years (50 ± 7); 26 patients were female (54.1%); mean BMI was 25 ± 4.7 kg/m². (Table 1.)

Out of 48 type 2 diabetic patients with secondary sulphonylureas failure who were shifted to repaglinide with metformin: 12 patients (25 %) achieved good control (mean FPG 121 ± 18 mg/dl) and 36 patients (75%) failed to get good control (mean FPG 229.3 ± 48.8 mg/dl).Table 2.

The insulin group consist 25 patients aged 35-55 years; 15 patients were female (60%). In this group, only 5 patients (20%) achieved good control (mean FPG 133.6 ± 6.3 mg/dl).Table 2.

The effect of sex, BMI and duration of DM on response of the patients with secondary sulphonylureas failure to repaglinide are shown in Table3

Table 1 Demographics of the repaglinide group patients.

Patients Characteristic		Result
mean age		50±7 year
Sex	Male	22(45.83%)
	Female	26(54.17%)
Mean Weight		67.5±13 Kg
Mean Height		164.20±5 cm
Mean BMI		25±4.7kg/ m ²
Mean of DM duration		8.8±5 yr

Table 2 Response of patients with secondary sulphonylureas failure to repaglinide and to insulin.

Type of treatment	Good control no (%)	Poor control no (%)	Total	P value
Repaglinide + metformin	12 (25)	36 (75)	48	< 0.05
Insulin	5 (20)	20 (80)	25	> 0.05

Table 3 Effect of sex, BMI and duration of DM on response to repaglinide.

Variable		Good control	Poor control	P value
Sex	Male	6	16	< 0.05
	Female	6	20	
BMI	< 30 kg/ m ²	7	12	< 0.05
	≥ 30 kg/ m ²	5	24	
Duration of DM	< 5 years	6	14	< 0.05
	≥ 5 years	6	22	

Discussion

Although the dose of repaglinide can be increased up to 16 mg/day, our patients are put on 3 mg/day because of limited supply of the drug from the diabetic center and high cost of the drug in the markets.

In this study there was significant response of patients with secondary sulphonylureas failure to repaglinide 3 mg/dl in divided doses. Though most of the studies reported parallel efficacy of repaglinide and sulphonylureas[7- 9], the difference in response in our study may be attributed

to superior glycemic control of repaglinide as claimed by others[6, 10].

Rushd Jibrán et al studied the efficacy and safety of repaglinide in comparison with glibenclamide in 100 newly diagnosed type 2 diabetic patients and followed up them for one year; at the end of the study they found the effect of repaglinide in lowering HbA1c was more potent than glibenclamide but both drugs were well tolerated and weight gain was minimal in both groups [6].

The response of the second group of patients with secondary sulphonylureas failure who put on

insulin was inadequate where only 20% of the patients achieved good diabetic control; in fact poor control of DM with in insulin therapy is found not only in these patient but in most patients with type 1 DM who are followed by the diabetic center; this observation may be due to poor compliance of the patients to repeated insulin injections, poor follow up and supply of different preparations of insulin to the same patient with different visits to the center.

There was significant effect of gender, BMI and duration of DM on the response of the patients to repaglinide. Better response of male patient may be due to biological difference in the metabolism of the repaglinide [13]. The response is less in obese patients probably due to higher incidence of insulin resistance in such patients. The longer duration of DM associated with poorer response to repaglinide; this is most likely due to greater damage of beta cells with time.

Conclusion

Repaglinide can induce good glycemic control in some patients with secondary sulphonylureas failure.

References

1. Silivio.E.Inzucchi; obert.S.Sherwen. Type 1 Diabetes Milletus. Goldman; Auseillo. Cecil medicin.23rd ed. Ch.247. 2007 online.
- 2.B.M.Frier; M.Fisher. Diabetes Mellitus. Davidson's Principles and practice of medicin.20th ed.p.817. 2006
3. Alvin .C.Power. Diabetes Mellitus. Harrison's principles of internal medicine.17th ed.Ch 338. 2008 online.
- 4.Silivio.E.Inzucchi, Robert.S.Sherwen. Type 2 Diabetes Mellitus, Goldman; Auseillo. Cecil medicin.23rd ed. Ch.248. 2007 online
5. Scheen AJ, Lefebvre PJ. Oral antidiabetic agents: a guide to selection. Drugs 1998; 55:225-36.
6. Rushid Jibrán; M.Imran Suliman; Fayyaz Quresi; Massod Ahmad. Safety and efficacy of repaglinide compared with glibenclamide in management of type 2 diabetic pakistani patients. Pak J med Sci.2006.Vol.22. NO.4 385-390
7. Culy CR, Jarvis B. Repaglinide: A review of its therapeutic use in type 2 diabetes mellitus. Drugs 2001; 61:1625-60.
8. Fuhlendorff J, Rolin B, MacKay P; et al. Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. Diabetes 1998; 47:345-51.
9. Hansen AMK, Christensen IT, Wahl P, et al. Repaglinide and nateglinide are differently affected by a single point mutation in SUR1/KIR6.2 CHANNELS. Diabetes 2001; 50 Suppl. 2:A9.
10. Michael T, Howard Weitz, Arnold A, et al. Diabetes Mellitus. MIKSAP 14. 2007 online
11. Perentesis GP, Damsbo P, Muller PG, et al. Single dose pharmacokinetics and pharmacodynamics of repaglinide in type 2 diabetic patients. J Clin Pharmacol 1994; 34:1021.
12. Owens DR, Luzio SD, Ismail I. Increased prandial insulin secretion after administration of a single preprandial oral dose of repaglinide in patients with type 2 diabetes. Diabetes Care 2000; 23:518-23.
13. Schumacher S, Abbasi I, Weise D, et al. Single-and multiple -dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. Eur J Clin Pharmacol 2001; 57:147-52.