

CLINICAL STUDY

Evaluation of the repaglinide efficiency in comparison to the glimepiride in the type 2 diabetes patients poorly regulated by the metmorfine administration

Dimic D, Velojic Golubovic M, Antic S, Radenkovic S

Clinical Center Nis, Clinic of Endocrinology, Diabetes and Metabolic Disorders, Nis, Serbia.

drdragand@bankerinter.net

Abstract: *Objectives:* An impaired early phase of insulin secretion in the type 2 diabetes mellitus (DM) is very important for the postprandial hyperglycemia. The aim of the study was to compare the efficacy of metformin/repaglinid and metformin/glimepirid regimes in type 2 diabetics uncontrolled with metformin monotherapy.

Methods: Totally, 60 type 2 diabetics with haemoglobin A1c $\geq 7.5\%$ and 2000 mg of metformin monotherapy for at least three months were divided in the following groups: A-30 patients with metformin+repaglinid (2 mg for each meal) and B metformin+glimepirid (3 mg in the morning). Assessment of the regimes efficacy comprised of haemoglobin A1c, fasting blood glucose (FBG) and postprandial blood glucose (PBG). Assessment of the safety was performed on the basis of recorded hypoglycemia (<4.0 mmol/l).

Results: In both groups, FBG was significantly lower at the end of the study. In the group A it decreased from 9.03 ± 1.00 to 7.32 ± 0.65 ($p < 0.001$), in the group B from 8.94 ± 1.01 to 7.23 ± 0.70 ($p < 0.001$). There was no statistical difference between the groups. PBG was significantly lower after 12 weeks in both groups.

Conclusion: Metformin/repaglinid is an efficient and safe therapeutic regime in the treatment of the type 2 DM that ensure a better control of PBG levels (Tab. 4, Ref. 18). Full Text (Free, PDF) www.bmj.sk.

Key words: diabetes mellitus type 2, hypoglycemic agents, therapy, postprandial regulation, haemoglobin A1c, repaglinid.

The type 2 diabetes mellitus (type 2 DM) is a heterogenous disorder characterized by a decrease of insulin secretion and insulin effect. It is a serious, progressive metabolic disease whose poor control is characterized by an acute and chronic hyperglycemia. Treatment strategy of this disease is a control of the blood sugar level, improvement of the insulin sensitivity and beta cell function, and resulting reduction of the micro and macro vascular complications. In persons suffering from this form of diabetes it is a disorder of an early phase of insulin secretion that plays the main role in the regulation of the postprandial glycemia causing excessive glycemic postprandial excursions. These secretion alterations occur very early in the pathogenetic process of the type 2 DM. The loss of the early phase of insulin secretion is determined as the main cause of the postprandial glucose intolerance (1). Postprandial glycemic peaks look like a prospective determinant of the vascular damage both from the very onset of the type 2 DM and also in the course of the impaired glucose tolerance (IGT). DECODE and other epidemiological studies pointed that the larger glucose excursions during IGT represent a better predictor of the cardiovascular risk compared to the

preprandial hyperglycemia. Prandial glucose tolerance represents a new concept in the type 2 DM treatment. Conventional therapy regimes were primarily designed to control the preprandial blood sugar level and haven't strictly insisted on the efficient postprandial control. The concept of the postprandial regulation aims to control the postprandial glycemies and to achieve all day, in longer course of time, good glycemic control. Poorly controlled postprandial hyperglycemia makes insulin resistance worse and causes a further insulin secretory capacity decrease.

Oral antidiabetics are divided, in accordance to the mechanism of action, to the insulin secretion stimulators and insulin action stimulators (5). As the majority of patients suffering from the type 2 DM have an increased insulin resistance and damaged insulin secretion, the rational approach to the therapy is a combination of a various agent's classes.

The American Diabetes Association and European Association for the Study of Diabetes from August 2006 have adopted a joint therapy consensus recommending metmorfine as a medication of the first choice in all the persons with the type 2 DM, including those not suffering from obesity (6, 7). It is estimated that the secondary failure of the metformine monotherapy isn't small, 5–10 % annually (5, 6). In patients where good metabolic control can't be achieved only by metformine administration, the adopted consensus recommends the induction of a new combined therapy (insulin secretagogos, tiazide and/or insulin). The most frequently applied combination is metformine-sulphonyl-

Clinical Center Nis, Clinic of Endocrinology, Diabetes and Metabolic Disorders, Nis, Serbia

Address for correspondence: D. Dimic, MD, PhD, Albanske Golgote 1/13, 18000 Nis, Serbia.
Phone: +381631094024

urea. Sulphonylurea drugs do not have a fast impact on the increase of postprandial glycaemia due to their slow action (low absorption level). Moreover, their extended effect significantly increases the hypoglycaemia risk, even in small doses (6, 8). As the metformine itself does not achieve the proper postprandial control, it is needed to administer faster and short-lasting stimulators of insulin secretion, as repaglinide. Repaglinide belongs to the family of meglitinides and to the first insulin secretagog designed to stimulate an early insulin secretion during postprandial period thus causing a reduction of postprandial hyperglycaemia and consequently decreasing 24 h basal glycaemic profile and reducing hemoglobin A1c level (HbA1c). Animal models and in vitro studies have proven that repaglinide shows a glucose-dependent activity and provokes insulin secretion only in the glucose presence. Opposite to the sulphonylurea drugs, it does not inhibit a glucose-stimulated insulin bio-synthesis in pancreatic islands and does not stimulate insulin secretion in glucose deficiency (1, 9, 10). In comparison to other secretagogues, repaglinide shows a similar antihyperglycaemic effect but significantly lower hypoglycaemia risk (7, 9, 11). Recently, it has been shown that repaglinide compared to gliburide in persons suffering from the type 2 DM causes a decrease of the intima-media of the carotid plaque and is distinguished as a significant insulin secretagog that does not affect only hyperglycaemia but also the cardiovascular risk (7).

The prime goal of our study was to compare the effects of the two different therapy regimes – metformine/glimepiride and metformine/repaglinide in glucose control in patients suffering from the type 2 DM, previously poorly managed by the metformine monotherapy, expressed by the values of the morning and postprandial glycaemia and HbA1c value. The secondary aim was a comparison of the safety of these two therapy regimes.

Methods

The research comprises 60 patients suffering from the type 2 Diabetes mellitus (type 2 DM) with values of glycosylated hemoglobin (HbA1c) $\geq 7.5\%$. All subjects underwent diet and a 2000 mg daily metformine therapy for at least three months in past. The study excluded patients with a clinically active cardiovascular disease (NYHA III and IV), including the date of an acute myocardial infarction and stroke in previous 6 months, altered kidney function (serum creatinine $\geq 135 \mu\text{mol/l}$), altered liver function (ALAT 2.5 x upper limit of normal) and the use of drugs that affect glucoregulation (glucocorticoides). The subjects were divided into two groups: the Group A (n=30), that beside fasting and metformine (2000 mg/day) introduced a 2 mg dose of repaglinide into the therapy before the main meals (6 mg/day), and the Group B (n=30), that beside fasting and metformine (2000 mg/day) therapy introduced a 3 mg of glimepiride as one morning dose. The patients have been monitored in the period of 12 weeks.

In all subjects, the values of HbA1c were evaluated at the beginning and after 12 weeks, daily profile of glucose at 6 points, before and after two hours from the main meals, total chole-

Tab. 1. Clinical characteristics of the patients.

	Group A	Group B
Number of patients	30	30
Age of patients (years)	57 \pm 3.2	59 \pm 4.7
Gender (m/f)	13/17	14/16
Duration of diabetes mellitus (years)	3.63 \pm 1.33	3.21 \pm 1.79

Group A – patients on metformin/repaglinid therapy. Group B – patients on metformin/glimepirid therapy

sterol, LDL and HDL cholesterol, triglycerides and body mass index (body weight/square body height, kg/m^2).

The therapy efficiency was evaluated on the base of glucoregulation parameters in both groups, i.e. HbA1c, morning fasting plasma glucose (FPG) and postprandial plasma glucose (PPG), glycaemia measured two hours after the beginning of the meal. Safety evaluation was evaluated on the base of the recorded hypoglycaemic episodes that were divided into moderate and serious. The moderate hypoglycaemias included implicitly the episodes when the patient did not require another person's help. The serious hypoglycaemias included implicitly the episodes when the patient was not able to help himself, i.e. the help of another person was needed. Only those episodes were recorded that had an objective confirmation of glycaemia lower than 4 mmol/l, apart from the symptoms' presence.

All monitored parameters were defined in the central laboratory. Glycaemia was defined by the UV method with hexokinase, while HbA1c was defined by the immunoinhibitory method. Both methods were conducted by the Olympus reagents on the Olympus AU400 gauge. For the self-control at home, the patients used the gauge for glycaemia self-control ACCU-CHEK(Roche Diagnostics).

For the definition of statistic differences in studied parameters before and after the therapy, the Student t-test was used.

Results

Clinical characteristics of the study subjects are shown in the Table 1, while the statistically significant differences haven't been defined for the one observed parameter.

The average values of morning glycaemia in the studied groups at the beginning and after 12 weeks are shown in the Table 2. The average values of morning glycaemia at the end showed a statistically highly significant reduction compared to the beginning in the Group A that administered metformine and repaglinide (with 9.03 \pm 1.00 on 7.32 \pm 0.65) ($p < 0.001$), and in the Group B that administered metformine and glimepiride (with 8.94 \pm 1.01 on 7.23 \pm 0.70) ($p < 0.001$). There was no statistically significant difference between the groups.

The average values of postprandial glycaemia in the studied groups at the beginning and after 12 weeks are shown in the Table 2. The average values of postprandial glycaemia showed a statistically highly significant reduction compared to the beginning in the group A that administered metformine and repaglinide

Tab. 2. Fasting and postprandial glucose at the beginning and after 12 weeks.

	Group A		Group B	
	beginning	after 12 weeks	beginning	after 12 weeks
Fasting blood glucose (mmol/l)	9.03±1.00	7.32±0.65*	8.94±1.01	7.23±0.70*
Postprandial glucose (mmol/l)	11.21±1.15	7.71±0.65 * †	11.16±1.27	9.32±0.80*

Group A – patients on metformin/repaglinid therapy. Group B – patients on metformin/glimepirid therapy, * p<0.05 in the beginning and after 12 weeks in the same group, † p<0.05 between the two groups

Tab. 3. Haemoglobin A1c and body mass index at the beginning and after 12 weeks.

	Group A		Group B	
	beginning	after 12 weeks	beginning	after 12 weeks
Haemoglobin A1c (%)	8.67±0.39	7.13±0.50 * †	8.63±0.42	7.59±0.63 *
Body mass index (kg/m ²)	29.63±1.77	30.12±1.60 * †	29.21±1.39	31.22±1.34 *

Group A – patients on metformin/repaglinid therapy. Group B – patients on metformin/glimepirid therapy, * p<0.05 in the beginning and after 12 weeks in the same group, † p<0.05 between the two groups

Tab. 4. Total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides at the beginning and after 12 weeks.

	Group A		Group B	
	beginning	after 12 weeks	beginning	after 12 weeks
Cholesterol (mmol/l)	6.55±1.19	5.78±1.48 *	6.34±1.15	5.89±1.40
LDL cholesterol (mmol/l)	4.24±1.00	3.58±1.17 *	4.22±0.97	3.67±1.05 *
HDL cholesterol (mmol/l)	1.7±0.17	1.04±0.15	1.02±0.14	1.03±0.12
Triglycerides (mmol/l)	3.90±1.33	3.24±0.79 *	3.74±1.38	3.34±1.07

Group A – patients on metformin/repaglinid therapy. Group B – patients on metformin/glimepirid therapy, * p<0.05 in the beginning and after 12 weeks in the same group

(with 11.21±1.15 at 7.71±0.65) (p<0.001) and in the group B that administered metformine and glimepiride (with 11.16±1.27 at 9.32±0.88) (p<0.001). By the comparison of the average values of postprandial glycemia between the groups, a statistically significant higher reduction was observed in the group of subjects treated by repaglinidine (p<0.001).

The average values of HbA1c in the studied groups at the beginning and after 12 weeks are shown in the Table 3. The average values of HbA1c showed a statistically highly significant reduction compared to the beginning in the group A that administered metformine and repaglinide (with 8.67±0.39 at 7.13±0.50) (p<0.001) and in the group B that administered metformine and glimepiride (with 8.63 at 7.59) (p<0.001). By the comparison of the average values of HbA1c between the groups, the statistically significant higher reduction of this parameter was observed in the group of subjects treated by repaglinidine (p<0.01).

The average values of body mass index at the beginning and after 12 weeks are shown in the Table 3. The average values of the body mass index showed a statistically high rise compared to the beginning in the group A that administered metmorfine and repaglinide (with 29.63±1.77 at 30.12±1.60) (p<0.05) and in the

group B that administered metformine and glimepiride (with 29.21±1.39 at 31.22±1.34) (p<0.001). By the comparison of the average values of the body mass index between the groups, a statistically significant rise of this parameter was observed in the group of subjects treated by glimepiride (p<0.01).

The average values of lipids parameters at the beginning and after 12 weeks are shown in the Table 4. The average values of lipids parameters, except for values of the HDL cholesterol, showed a statistically significant reduction at the end compared to the beginning in the group A that administered metformine and repaglinide (p<0.05). In the group B that administered metformine and glimepiride, there was a reduction of the average value of lipids parameters, but the statistical significance was achieved only in reduced values of the LDL cholesterol (p<0.05). There was no statistically significant difference between the groups.

The safety evaluation was based of the recorded hypoglycemia episodes. There were no serious hypoglycemia episodes in both groups. In the Group A, 5 episodes were recorded in 5 patients. In the Group B, 7 hypoglycemia episodes were recorded in 7 patients that mean no significant difference.

Discussion

Diabetes is a chronic, progressive disease with a high risk of cardiovascular diseases. Hyperglycemia, as a basic metabolic disorder in diabetes, plays a significant role in the development of cardiovascular diseases. Insulin secretion in healthy persons is biphasic, with early, fast, and late, slow phase. In the type 2 diabetes, insulin secretion is altered by slowing and shortening of the early, fast phase and extending of the late secretion phase. This secretion disorder results in the increase of hepatic glucose production and pronounced hyperglycemia after meals. Postprandial hyperglycemia results from the absence of suppression of hepatic glucose production, a decrease in the peripheral take-over of glucose and decrease of pancreas insulin secretion (1). There are more and more evidence that postprandial hyperglycemia significantly contributes to the development of atherosclerosis, where fast and large leap of the blood sugar level after meal is an important factor in the pathogenetic mechanism of chronic complications of diabetes mellitus (4, 12).

Diabetes Intervention Study has shown the existence of the relationship between preprandial and postprandial glycemia and myocardial infarction and death, where only the impact of postprandial glycemia reaches a statistic significance (4).

Therapy approach to the type 2 diabetes mellitus is based on beta cells secretion stimulation by insulin secretagogues. Former therapy regimes were primarily designed for the control of preprandial glycemia values and did not successfully controlled postprandial glucose excursions. Repaglinide is the first insulin secretagogue that stimulates the early phase of insulin secretion in postprandial period, without a prolonged stimulation during the period of hunger (10, 13, 14).

Former studies showed that the effect of the combined therapy metformine and repaglinide is better compared to the individual application of these drugs. The significant decrease of HbA1c was achieved, while up to 60 % of patients reached the values of HbA1c below 7 % (2, 5). Available data suggest that this combination provide equally good results in glucose regulation compared to the traditional regimes of combined therapy (metformine-sulphonylurea) (15). Comparison of repaglinide to the treatment by sulphonylurea medications showed a similar efficiency in the view of regulation of morning glycemia values, while only repaglinide statistically significantly reduced the values of 2 h postprandial glucose (3).

The analysis of our results showed an improvement of the glycemic control in both groups, with a statistically significant difference in all studied parameters before and after the therapy. Both therapy regimes achieve a significant decrease of morning glycemia values, without a statistically significant difference between them. The effect of repaglinide on the early phase and a significant increase of insulin secretion during the first 30 minutes (13) resulted in a significant difference in decreasing the values of postprandial glycemia that gives an advantage of this therapy compared to the conventional one. There was also a statistically significant higher reduction of HbA1c in the Group A with metformine/repaglinide therapy.

Despite a better control of glycemia, the short-lasting insulin secretagogues enable better body weight control. Different to glibenclamide, netaglinide in various studies did not lead to the body weight increase (1, 2, 3, 5). Repaglinide resulted in a significant body weight increase (2), while a significant increase of the body mass index in the group with glimepiride therapy was shown. Other authors did not observe alterations of the lipids status in patients with repaglinide therapy compared to glibenclamide (3). Repaglinide showed a minimum effect on HDL cholesterol, while some authors noticed triglyceride reduction (1). Our subjects showed a decreased trend of lipids parameters, reaching significances only for LDL cholesterol without a significant differences between groups.

Hypoglycemia is the most frequent undesired event in anti-diabetics application. Symptomatic hypoglycemia is more frequent in patients with combined therapy, metformine/repaglinide (up to 33 %) compared to monotherapy with repaglinide (10.7 %) or metformine (0 %), although recent data showed that metformine itself possesses a potential to induce hypoglycemia (3, 5, 7). Repaglinide and medications of second generation of sulphonylurea showed a similar risk of hypoglycemia (3, 16, 17). The frequency of hypoglycemia in repaglinide therapy is similar, in some cases even lower, with a risk reduction of 51 %, compared to patients with glibenclamide therapy (18). Severe hypoglycemias were recorded in only 0.3 % of patients with repaglinide therapy (9). Our results did not show significant differences in the frequency of hypoglycemia between the studied groups, with a negligible higher frequency in the group with metformine/glimepiride combination therapy.

Based on above there are numerous evidences that the combination of oral anti-diabetics with complementary action mechanism is highly efficient in achieving and maintaining good glycemic control. Good combined therapy should decrease clinical symptoms, improve the quality of life, establish euglycemia both preprandial and postprandial without increasing the risk of hypoglycemia, and prevent or postpone chronic diabetes complications. Prandial glucose regulation represents a new concept in the type 2 diabetes therapy. By the reduction of postprandial glucose excursions, the good diabetes control is achieved in long term, leading to the prevention of diabetes complications.

Repaglinide is the first prandial glucose regulator characterized by fast and short insulintropic effect, by which it reduces postprandial glucose oscillations in superior manner than other insulin secretagogues, not increasing the risk of hypoglycemia. Repaglinide is very efficient in combined therapy in patients with the type 2 diabetes that require more intensive therapy.

Based on obtained results and data from literature, metformine/repaglinide combination represents an efficient and safe therapy regime in the treatment of patients with the type 2 diabetes that provides a better postprandial glucose control.

References

1. Li J, Tian H, Li Q, Wang N, Wu T, Liu Y et al. Improvement of insulin sensitivity and β -cell function by nateglinide and repaglinide in type 2 diabetic patients — a randomized controlled double-blind and double-dummy multicentre clinical trial. *Diabetes Obes Metab* 2007; 9: 558–565.

2. **Standl E, Fuchtenbusch M.** The role of oral antidiabetic agents: why and when to use an early-phase insulin secretion agent in Type 2 diabetes mellitus. *Diabetologia* 2003; 46 (1): 30-3-6.
3. **Owens DR, McDougall A.** Repaglinide: prandial glucose regulation in clinical practice. *Diabetes Obes Metab* 2000; 2 (2): 43—48.
4. **Home PD.** Postprandial hyperglycemia: mechanisms and importance. *Diabetes Obes Metab* 2000; 2 (1): 7—11.
5. **Van Gaal LF, De Leeuw IH.** Rationale and options for combination therapy in the treatment of Type 2 diabetes. *Diabetologia* 2003; 46 (1): 44—50.
6. **Garber AJ.** Using dose-response characteristics of therapeutic agents for treatment decisions in type 2 diabetes. *Diabetes Obes Metab* 2000; 2: 139—147.
7. **Lund SS, Tarnow L, Stehouwer CDA, Schalkwijk CG, Frandsen M, Smidt UM et al.** Targeting hyperglycaemia with either metformin or repaglinide in non-obese patients with type 2 diabetes: results from a randomized crossover trial. *Diabetes Obes Metab* 2007; 9: 394—407.
8. **Hermann LS, Lindberg G, Lindblad U, Melander A.** Efficacy, effectiveness and safety of sulphonylurea-metformin combination therapy in patients with type 2 diabetes. *Diabetes Obes Metab* 2002; 4: 296—304.
9. **Marshall V, Wilton I, Shakir S.** Safety profile of repaglinide as used in general practice in England: results of a prescription-event monitoring study. *Acta Diabetol* 2006; 43: 6—13.
10. **Ozbek M, Erdogan M, Karadeniz M, Cetinkalp S, Ozgen AG, Saygili F et al.** Preprandial repaglinide decreases exogenous insulin requirements and HbA1c levels in type 2 diabetic patients taking intensive insulin treatment. *Acta Diabetol* 2006; 43: 148—151.
11. **Civera M, Merchante A, Salvador M, Sanz J, Martinez I.** Safety and efficacy of repaglinid in combination with metformin and bedtime NPH insulin as an insulin treatment regimen in type 2 diabetes. *Diabetes Res Clin Pr* 2008; 79: 42—47.
12. **Ceriello A.** Postprandial hyperglycemia and diabetes complications. Is it time to treat? *Diabetes* 2005; 54: 1—7.
13. **De Souza CJ, Russo P, Lozito R, Dunning BE.** Differential effects of short and long duration insulinotropic agents on meal-related glucose excursions. *Diabetes Obes Metab* 2001; 3: 78—83.
14. **Moses RG, Gomis R, Frandsen KB, Schlienger JL, Dedov I.** Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. *Diabetes care* 2001; 24: 11—15.
15. **Monami M, Luzzi C, Lamanna C, Chiasserini V, Addante F, Desideri CM et al.** Three-year mortality in diabetic patients treated with different combinations of insulin secretagogues and metformin. *Diabetes Metab Res Rev* 2006; 22: 477—482.
16. **Schumacher S, Abbasi I, Weise D, Hatorp V, Sattler K, Sieber J 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—152.
17. **Van Gaal LF, Van Acker KL, De Leeuw IH.** Repaglinid improves blood glucose control in sulphonylurea-naive type 2 diabetes. *Diabetes Res Clin Pr* 2001; 53: 141—148.
18. **Papa G, Fedele V, Rizzo MR, Fioravanti M, Leotta C, Solerte SB et al.** Safety of type 2 diabetes treatment with repaglinide compared with glibenclamide in elderly people. *Diabetes Care* 2006; 29: 1918—1920.

Received October 15, 2008.

Accepted March 6, 2009.