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EFEKAT REPAGLINIDA NA PRVU FAZU SEKRECIJE INSULINA KOD OSOBA SA NARUŠENOM HOMEOSTAZOM GLIKOZE

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THE EFFECT OF REPAGLINIDE ON THE FIRST PHASE OF INSULIN SECRETION IN PERSONS WITH IMPAIRED GLUCOSE HOMEOSTASIS

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SAŽETAK

Uvod: *Progresija od normalne ka narušenoj homeostazi glikoze (IGH) i, najzad, dijabetesu je udružena sa redukcijom senzitivnosti na insulin i progresivnom smanjenju akutnog insulinskog odgovora na glikozu (prva faza sekrecije insulina), koja je potpuno ugašena u trenutku nastupa dijabetesa. Repaglinid je insulinotropni agens kratkog dejstva koji stimuliše sekreciju insulina i koji ima novi profil oslobađanja insulina.*

Cilj: *Cilj ovog istraživanja je bio da se utvrdi da li jednokratna primena Repaglinid-a može da koriguje prvu fazu sekrecije insulina kod osoba sa IGH.*

Metod: *Pet pacijenata sa IGH je obuhvaćeno ovom studijom. Insulinska sekrecija je ispitivana intravenskim testom tolerancije glikoze sa učestalim uzimanjem uzoraka (FSIVGTT). Svaki pacijent je podvrgnut, tokom dva sukcesivna dana, ovom testu, prvog dana je izvođen regularan FSVGTT, a sledećeg dana modifikovani FSIVGTT (30 min pre davanja glikoze pacijenti su per os uzimali 1,0 mg Repaglinid-a.*

Rezultati: *Pokazano je da Repaglinid povećava prvu fazu sekrecije insulina: površina ispod krive insulinemije tokom prvih 10 minuta nakon primene glikoze (pre 82.96 ± 77.04 vs posle 377.88 ± 374.33, p = 0.043) i ukupan zbir insulinemije u prvom i trećem minutu FSIVGTT-a (pre 53.54 ± 39.64 vs posle 127.04 ± 100.60, p = 0.043). Repaglinide ne utiče statistički značajno na drugu fazu sekrecije insulina kod osoba sa IGH. Takođe, kod ovih pacijenata, Repaglinid nije statistički značajno menjao metabolizam glikoze (procenjeno preko površine ispod krive glikemije tokom FSIVGTT-a, poluvremena iščezavanja glikoze ($T_{1/2}$) i Conard-ove konstante).*

Zaključak: *Repaglinid povećava prvu (ali ne i drugu) fazu sekrecije insulina u osoba sa IGH. Premedikacija Repaglind-om ne utiče na metabolizam glikoze.*

Ključne reči: *sekrecija insulina, narušena homeostaza glikoze, repeglinid, diabetes mellitus*

ABSTRACT

Introduction: *The progression from normal to impaired glucose homeostasis (IGH) and, finally diabetes is associated with a reduction in insulin sensitivity and a progressive decrease of the acute insulin response to glucose (the first phase of insulin secretion), which is lost at the onset of diabetes. Repaglinide is a short-acting, insulinotropic antidiabetic agent which stimulates insulin secretion and which has a novel insulin release profile.*

Aim: *The aim of this study was to investigate whether a single use of Repaglinide can correct the first phase of insulin secretion in persons with IGH.*

Method: *Five patients with IGH were included in the study. Insulin secretion was assessed by the frequently sampled intravenous glucose tolerance test (FSIVGTT). Each one underwent two FSIVGTT performed on two successive days, one day regular FSIVGTT and the day after, FSIVGTT modified by premedication 1,0 mg of Repaglinide.*

Results: *It was demonstrated that Repaglinide increases the first phase of insulin secretion: area under the curve of insulin of the plasma insulin concentration in the first 10 min after the administration of glucose (before 82.96 ± 77.04 vs after 377.88 ± 374.33, p = 0.043) and the total sum of insulinemia in the first and the third minutes of FSIVGTT (before 53.54 ± 39.64 vs after 127.04 ± 100.60, p = 0.043). Repaglinide does not influence the second phase of insulin secretion in persons with IGH. Also, in these patients, Repaglinide doesn't change significantly the metabolism of glucose (assessed by area under the curve of glucose during FSIVGTT, half-time of glucose disappearance rate ($T_{1/2}$) and Conard's constant).*

Conclusion: *Repaglinide increases the first (but not the second) phase of insulin secretion in persons with IGH. The metabolism of glucose was not affected by Repaglinide premedication.*

Key words: *insulin secretion, impaired glucose homeostasis, repaglinide, diabetes mellitus*

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INTRODUCTION

Type 2 (noninsulin-dependent) diabetes is a major cause of mortality and morbidity worldwide (the prevalence is rising rapidly in association with 'westernization' of lifestyle and dietary habits) (1). Understanding of the pathophysiological basis of this condition is a prerequisite for the development of improved options for both treatment and prevention. Patients with established diabetes mellitus type 2 display impairments of both insulin action and secretion, but the primary abnormality (or abnormalities) in the evolution of type 2 diabetes remains unclear (2). Otherwise, hyperglycemia itself can affect both insulin sensitivity and β-cell function (3) and studies of subjects with established type 2 diabetes are likely to be inconclusive with respect to identification of the earliest metabolic defects. The American Diabetes Association (ADA) (4) and the World Health Organization (WHO) (5) have revised the diagnostic criteria of diabetes and glucose intolerance. A new category of impaired glucose homeostasis (IGH) represents impaired fasting glucose (IFG, when fasting blood glucose is 6.1-6.9 mmol/L) and/or impaired glucose tolerance (IGT, when 120 min glucose is 7.8-11.1 mmol/L). It has been shown that progression from normal to impaired glucose homeostasis and, finally diabetes is associated with a reduction in insulin sensitivity and a progressive decrease of the acute insulin response to glucose (the first phase of insulin secretion), which is lost at the onset of diabetes (6,7). Thus, low first-phase insulin release is an early abnormality in deteriorating glucose homeostasis and late-phase insulin release is more prolonged, but of less amplitude (8).

Repaglinide, a carbamoylmethyl benzoic acid derivative, is a short-acting, insulinotropic antidiabetic agent. In vitro studies of mouse and rat pancreatic ß-cells indicate that Repaglinide is potent in inhibiting ATP-sensitive potassium channels, increasing intracellular concentrations of calcium, and stimulating insulin release. It is a prandial glucose regulator and the first in a new chemical class of insulin secretagogues (meglitinide, a new type of oral antidiabetic agent). Although Repaglinide, like the sulfonylurea drugs, stimulates insulin secretion by pancreatic ß-cells, it acts via a different binding site on the ATP-sensitive potassium channel (9). Rapid absorption of Repaglinide, its short metabolic half-life (~1 h) (10) and a novel insulin release profile (11) are all characteristics desired for treating patients with diabetes mellitus type 2. The use of Repaglinide with each main meal of the day acts to augment insulin release, covering the glucose load associated with meals.

AIM

The purpose of the present study was to investigate whether the single use of Repaglinide can correct the first phase of insulin secretion in persons with IGH.

PATIENTS AND METHODS

Subjects

Five patients with IGH were included in the study. All subjects were confirmed to be free of severe systemic (cardiac, renal, hepatic, cerebrovascular, thyroid, or adrenal) disease and were not taking any drugs or hormone known to influence carbohydrate or lipid metabolism. All subjects in the study gave their informed, written, voluntary consent, and our institutional ethics committee approved the study protocol.

Protocol

After the initial evaluation, the diagnosis of IGH (IFG and/or IGT) was established by a 75-g oral glucose tolerance test (OGTT), according to the criteria of the American Diabetes Association (4). All subjects were asked to consume a diet with normal contents of carbohydrates for 3 days before testing Each one underwent two FSIVGTT performed on two successive days, one day regular FSIVGTT and the day after, FSIVGTT modified by Repaglinide premedication.

Assessment of insulin secretion

Insulin secretion was assessed by the frequently sampled intravenous glucose tolerance test (FSIVGTT) (12) as previously described. Also, a reduced sampling protocol, requiring 14 plasma samples was used. At 8:00-9:00 A.M, after a 12-h overnight fast, blood samples (for the determination of plasma glucose and insulin concentrations) were collected at 30 min, immediately before (0 min) and immediately after (0' min) the infusion of glucose (in the form of a 25% solution (0.5 g/kg) over 2 min), and 1, 3, 5, 10, 20, 30, 40, 50, 60, 90 and 120 min after the end of glucose infusion.

During FSIVGTT modified by premedication of Repaglinide, patients received 1mg Repaglinide p.o. (NovoNorm 1mg, Novo Nordisk®, Denmark) 30 min before infusion of glucose.

The insulin secretion was assessed separately for the first and the second phase. The first phase of insulin secretion or acute insulin response to glucose was calculated:

- the mean insulin increment (area under the curve of insulin, AUC calculated by the trapezoid rule) in the plasma insulin concentration above the basal (the mean insulin at -30 to 0 min) in the first 10 min after the administration of glucose (13).

- the total sum of insulinemia in the first and the third minute of FSIVGTT.

The second phase of insulin secretion was calculated as the incremental area under the curve (AUC; calculated by the trapezoid rule) from 10 to 120 min of the FSIVGTT.

The glucose metabolism was assessed by:

- half-time of glucose disappearance rate (T1/2) was calculated from the slope of glucose decline from 0' to 60 min of the FSIVGTT

- Conard's constant was calculated towards (0.693 x 100) / T1/2 and

- as the total area under the curve of glycemia (AUC; calculated by the trapezoid rule) from 0' to 120 min of the FSIVGTT

Assays

Serum glucose was assayed by the glucose oxidase method within 1h of the sample collection, using an automatic analyzer (Olympus, AU640, Medicon). Serum samples were stored at -40^{3}C until they were assayed for insulin by a radio immunoassay (MP Biomedicals - Orangeburg, USA). This assay is specific for insulin and does not recognize proinsulin. Intra- and interassay coefficients of variation were 5.4 and 6.4%, respectively, and the sensitivity of the method was 4.2 mIU/mL.

Statistical Analysis

All data are expressed as means Ò SEM or means Ò SD. Student's t test was used for parametric and Mann-Whitney U test for nonparametric evaluation of differences between groups. Paired t test was used for evaluation of differences between time points within the same group during the follow-up. Statistical significance was set at $p < 0.05$.

RESULTS

The movements of glucose during regular and, by Repaglinide, modified FSIVGTT were shown on Figure 1.

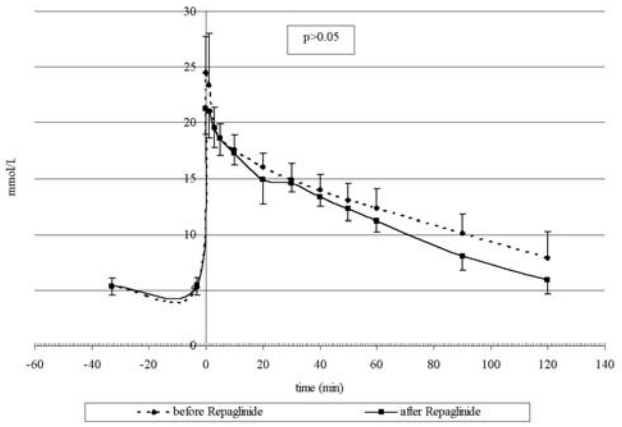

Figure 1. The movements of glucose during regular FSIVGTT and FSIVGTT modified by premedication of Repaglinide

Half-time of glucose disappearance rate during the first hour of glucose loading was 64.59 ± 12.95 min during regular FSIVGTT and 68.52 ± 13.38 min during modified FSIVGTT ($p>0.05$). Similarly, there isn't statistically significant change of Conard's constant (1.107 ± 0.217 vs 1.046 ± 0.230, before and after Repaglinide, respectively, $p>0.05$). Also, we didnžt find any statistically significant difference between total area under the curve of glycemia during regular and modified FSIVGTT (1245.42 ± 390.36 vs 1137.34 ±461.36, before and after Repaglinide, respectively, $p>0.05$). Thus, T1/2, Conard's constant and total area under the curve of glycemia were not changed after premedication by Repaglinide (Table 1).

parameters	Before Repaglinide	After Repaglinide	Probability
$T_{1/2}$ (min)	64.59 ± 12.95	68.52 ± 13.38	p > 0.05
Conard`s constant	1.107 ± 0.217	1.046 ± 0.230	p > 0.05
AUC[1] of glycemia	1245.42 ± 390.36	1137.34 ± 461.36	p > 0.05

[1]AUC - the total area under the curve

Table 1. The parameters of glucose metabolism during FSIVGTT

There was no difference in parameters of glucose metabolism during regular and Repaglinide premedication modified FSIVGTT.

The first phase of insulin secretion was diminished in persons undergoing this investigation. Repaglinide premedication increases parameters of the first phase of insulin secretion (Figure 2 and 3).Area under the curve of insulin above the basal in the first 10 min after the administration of glucose was increased after the administration of Repaglinide before testing (82.96 ±77.04 vs 377.88 ± 374.33, $p=0.043$) (Figure 4). The sum of insulinemia in the first and the third minutes of FSIVGTT was significantly higher after taking 1,0 mg Repaglinide (53.54 ± 39.64 vs 127.04 ± 100.60, $p=0.043$) (Figure 5).

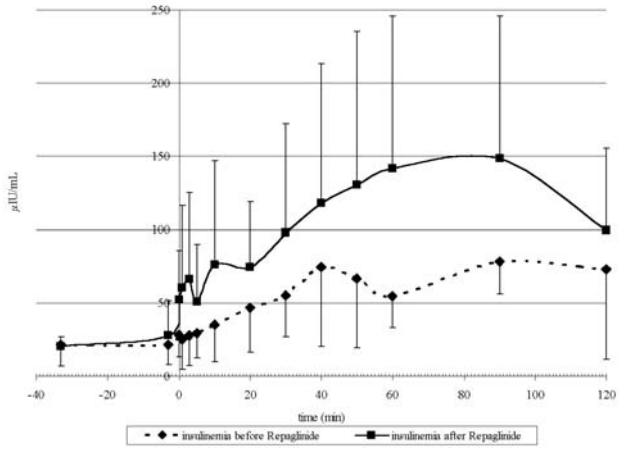

Figure 2. The movements of insulinemia during regular FSIVGTT and FSIVGTT modified by premedication of Repaglinide

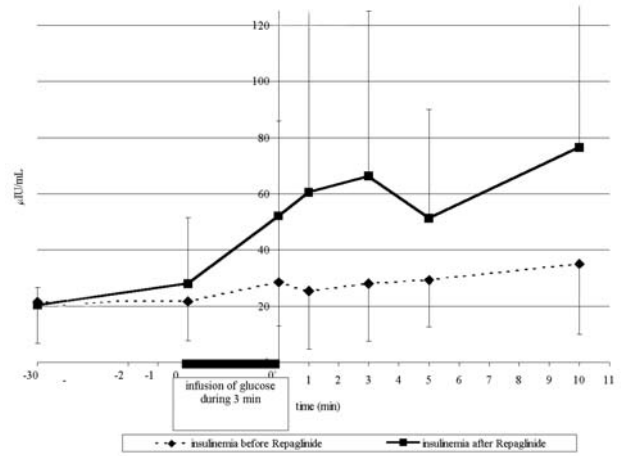

Figure 3. The movements of insulinemia during first 10 minutes after glucose infusion of regular FSIVGTT and of FSIVGTT modified by premedication of Repaglinide (p=0.043)

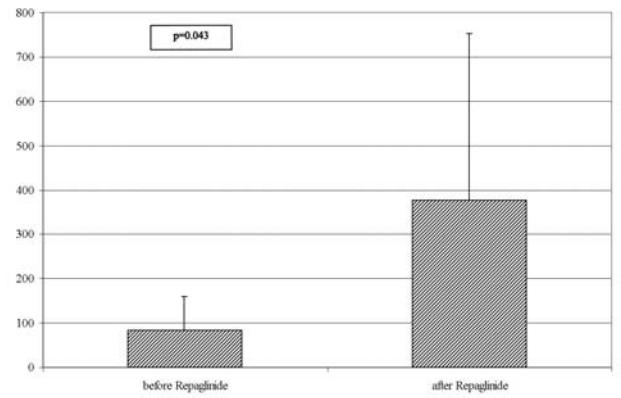

Figure 4. The mean insulin increment (area under the curve of insulin, AUC calculated by the trapezoid rule) in the plasma insulin concentration above the basal (the mean insulinemia at -30 to 0 min) in the first 10 min after the administration of glucose (p=0.043)

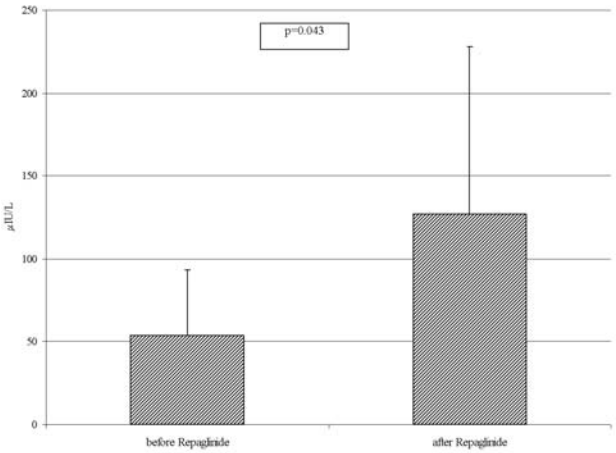

Figure 5. The total sum of insulinemia in 1. and 3. min after administration of glucose during FSIVGTT (p=0.043).

The second phase of insulin secretion (calculated as the incremental area under the curve from 10 to 120 min of the FSIVGTT) increased also, but it didn't reach statistical significance (4.235.30 ± 1443.88 vs 9278.70 ± 6445.39, p>0.05).

DISCUSSION

It is known that insulin release by pancreatic β-cells is controlled in part by the cellular membrane potential, which depends on the activity of ATP-sensitive potassium channels in the plasma membrane and on extracellular glucose concentrations (14). ATP-sensitive potassium-channel activity is high at low glucose concentrations, and the membrane on pancreatic β-cells is repolarized (electrically inactive) (15) At higher glucose concentrations, ATP-sensitive potassium channels close, depolarizing the β-cell membrane and opening voltage-dependent calcium channels (L-type). The increased calcium influx induces insulin secretion (exocytosis of insulin granules) (16). Functioning pancreatic β-cells are required for Repaglinide's antihyperglycemic activity since the drug lowers blood glucose concentrations principally by augmenting endogenous insulin secretion from the pancreas (17). Studies of pancreatic islet-cell cultures indicate a glucose-dependent relationship for the insulinotropic action of Repaglinide. Repaglinide does not stimulate insulin release in the absence of glucose (unlike sulfonylurea antidiabetic agents), and insulin release is diminished at low glucose concentrations (9). As blood glucose concentrations increase, Repaglinide augments the glucose-induced closure of ATP-sensitive potassium channels and, thereby, the release of insulin. However, Repaglinide exerts most of its insulinotropic activity at intermediate glucose concentrations (3.0-10.0 mmol/L). At high glucose concentrations (exceeding 15.0 mmol/L),

addition of Repaglinide does not augment the insulin release already stimulated by high extracellular glucose concentrations.

The results of this study show that movements of glucose during regular and, by Repaglinide modified FSIVGTT are similar. Beside glucose-dependent insulinotropic action, it is possible due to the fact that Repaglinide strengthens the oscillatory patterns of insulin secretion (this agent seems "more physiological" than the other groups of insulin secretagogues). (18)

It is clearly demonstrated in this study that single use of 1 mg of Repaglinide 30 min before glucose loading enhances the first phase, but it does not affect the second phase of insulin secretion in persons with IGH (they have diminished the first phase of insulin secretion).

The possible reasons for this are the following: rapid absorption, short time to reach peak concentration, short half-life of this drug (19), and its "more physiological" effect on insulin secretion (19). Repaglinide is rapidly and completely absorbed from the digestive tract following oral administration. In healthy men who received a 2-mg radiolabeled dose of Repaglinide during a multiple-dose study (2 mg 4 times daily for 13 days), the peak plasma concentration of Repaglinide averaged 27.7 ng/mL with an average time to peak concentration of 0.5 hours. Repaglinide is rapidly metabolized by the cytochrome P-450 (CYP) microsomal isoenzyme 3A4, principally via oxidation and dealkylation to the major dicarboxylic acid derivative (M2) and by further oxidation to an aromatic amine derivative (M1). An acyl glucuronide metabolite (M7) is formed from the carboxylic acid group of Repaglinide; a number of other unidentified metabolites also have been detected. The metabolites of Repaglinide do not have clinically important hypoglycemic activity. The elimination half-life of Repaglinide is about 1 hour when the drug is given in doses of 0.5-4 mg in healthy individuals and patients with diabetes mellitus type 2 (20-22).

CONCLUSION

Repaglinide increases the first phase, but it does not influence the second phase of insulin secretion in persons with IGH. In these patients, Repaglinide doesn't change significantly the metabolism of glucose. The feasibility to enhance and improve the β-cell secretory burst by an oral hypoglycaemic agent opens up a new insight into both, therapeutic and preventive approaches to diabetes mellitus type 2.

REFERENCES

1. O'Rahilly, S. Science, medicine, and the future. Non-insulin dependent diabetes mellitus: the gathering storm. British Medical Journal 1997; 314: 955-9
2. DeFronzo, R.A. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1998; 37: 667-87.
3. Yki-Jarvinen, H. Glucose toxicity. Endocrine Review 1992; 13: 415-431.
4. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20:1183-97.
5. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications: Diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. Diabet Med 1998; 15: 539-53
6. Brunzell JD, Robertson RP, Lerner RL, et al. Relationship between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. J Clin Endocrinol Metab 1976; 42: 222-9.
7. Weir GC, Bonner-Weir S: Insulin secretion in non-insulin-dependent diabetes mellitus. In Le Roith D, Taylor SI, Olefsky JM, Eds. Diabetes Mellitus. 2nd ed. Philadelphia, Lippincott, Williams and Wilkins, 2000: 595-603
8. Godsland LF, Jeffs JAR and Johnston DG. Loss of beta cell function as fasting glucose increases in the non diabetic range. Diabetologia 2004; 47: 1157-66
9. Fuhlendorff J, Rorsman P, Kofod H, et al. Stimulation of insulin release by Repaglinide and glibenclamide involves both common and distinct processes. Diabetes 1998; 47:345-51.
10. Wolffenbuttel BH, Nijst L, Sels JP, et al. Effects of a new oral hypoglycemic agent, Repaglinide, on metabolic control in sulphonylurea-treated patients with NIDDM. Eur J Clin Pharmacol 1993; 45: 113-6.
11. Graul A, Casta·er J: Repaglinide. Drugs Future 1996; 21:694-9.
12. Bergman RN, Finegood DT, Ader M: Assessment of insulin sensitivity in vivo. Endocr Rev 1985; 6:45 -86.
13. Chen M , Porte D Jr The effect of rate and dose of glucose infusion on the acute insulin response in man. Journal of Clinical Endocrinology and Metabolism 1976; 42: 1168-75.

14. Malaisse WJ. Stimulation of insulin release by non-sulfonylurea hypoglycemic agents: the meglitinide family. Horm Metab Res 1995; 27 (6): 263-6
15. Dornhorst A. Insulinotropic meglitinide analogues. Lancet 2001; 358 (9294): 1709-16
16. Davies MJ. Insulin secretagogues. Curr Med Res Opin 2002; (18)Suppl. 1: s22-30
17. Malaisse WJ. Mechanism of action of a new class of insulin secretagogues. Exp Clin Endocrinol Diabetes 1999; 107 Suppl. 4: S140-3
18. Juhl CB, P rksen N, Hollingdal M et al. Diabetes Care 2000; 23: 675-81.
19. Plosker LG and Figgitt PD. Repaglinide: a pharmacoeconomic review of its use in type 2 diabetes mellitus. Pharmacoeconomics 2004; 22(6): 389-411.
20. Hatorp V. Clinical pharmacokinetics and pharmacodynamics of Repaglinide. Clin Pharmacokinet 2002; 41 (7): 471-83.
21. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. Drugs 2001; 61 (11): 1625-60 .
22. Novo Nordisk. Prandin (Repaglinide) prescribing information (revised package insert). Princeton (NJ): 2003.