Effects of repaglinide vs glimepiride on serum glucose concentrations, HbA1c and body weight in patients with type 2 diabetes mellitus

Shatha Hani Mohamad.
Department of Pharmacology, College of Medicine, Mosul, Iraq.

Abstract

The present study was designed to compare the efficacy of repaglinide and glimepiride in patients with type 2 DM. The study included 61 type 2 diabetic patients already on metformin therapy (850 mg daily). The primary efficacy end points for comparison were final serum glucose concentrations, and HbA1c and changes in Serum glucose concentrations and HbA1c values from baseline. Repaglinide or glimepiride had been added to metformin in order to control patient's hyperglycemia. Repaglinide was used in a daily divided dose of 5mg before meals, 2mg at morning, 1mg afternoon, and 2mg at evening. Glimpiride was used in a daily dose of 4mg before lunch. Serum glucose concentrations was measured by using enzymatic colorimetric method and HbA1c was measured by using a commercial kit supplied by STANBIO laboratories, USA.

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels (1). Diabetes is often not diagnosed until complications appear, and approximately 30% of people with diabetes may be undiagnosed(2). Existing diagnostic methods include plasma glucose specific tests (fasting plasma glucose or oral glucose tolerance test) and glycated hemoglobin A1c (HbA1c), although the last method has not been recommended as a diagnostic tool mainly owing to the lack of standardized results (3).

A great deal of debate exists regarding the best initial oral therapy for patients with type 2 diabetes mellitus. The Agency for Healthcare Research and Quality (AHRQ) reviewed the published evidence regarding the comparative effectiveness of oral diabetes medication; the agency found little evidence to support predictions as to whether a particular medication is more likely to be effective in a given patient subgroup or to cause adverse effects in a particular patients (4). The AHRQ concluded that when used as a

monotherapy, most oral diabetes medications produce similar reductions in HbA1c, and that older medications e.g. metformin and second generation sulfonyl ureas can reasonably be used before newer ones e.g. glitazone and meglitinides, especially when cost is a factor (4).

Repaglinide, a short-acting meglitinide analogue, is a novel antidiabetic agent used to normalize postprandial glucose concentrations in patients with type II diabetes(5). It acts by enhancing glucose-stimulated insulin release from the pancreas, and its efficacy is dependent on the residual β-cell function of pancreatic islets(6). Repaglinide(7) undergoes marked first-pass metabolism, resulting in an oral bioavailability of approximately 60%. Repaglinide is completely metabolized and inactive metabolites are excreted primarily into faeces (8).

Glimperide is a sulphonylurea agent that stimulates insulin release from pancreatic beta-cells and may act via extrapancreatic mechanisms. It is administered once daily to patients with type2 diabetes mellitus in whom hyperglycemia is not controlled by diet and exercise alone, and may be combined with insulin in patients with secondary sulphonylurea failure. In patients with type type 2 diabetes, glimepiride has an effective dosage range of 0.5 to 8 mg/ day. Glimepiride was similar in efficacy to glibenclamide and glipizide in 1-year studies. Pooled clinical trial data suggest that glimepiride may have a lower incidence of hypoglycaemia than glibenclamide, particularly in the first month of treatment (9).

Since no clinical trial was conducted to compare the efficacy of repaglinide and glimepiride in the treatment of type 2 diabetic patients, so the present study was designed to compare the efficacy of this drugs in patients with type 2 DM.

Patients and Methods

This study was open, controlled, for comparison of repaglinide and glimpiride treatment on serum glucose concentrations, HbA1c and body weight of the patients for a period of 16 weeks. The study included 61 type 2 diabetic patients already on metformin therapy (850 mg daily). The study was started at March/ 2010 and ended at February/ 2011.The primary efficacy end points for comparison were final serum glucose concentrations, and HbA1c and changes in Serum glucose concentrations and HbA1c values from baseline. Enrolled patients were adults (mean age for repaglinide =49.15 years and for glimpiride 52.43 years) type 2 diabetic patients who had been treated with only metformin during the previous 3 months and had poor or fair glycemic control.

Repaglinide or glimpiride had been added to metformin in order to control patient's hyperglycemia. Repaglinide (Novonorm, Novonordisk, Saglikurunleri, Turkey, Istanbul) was used in a daily divided dose of 5mg before meals, 2mg at morning, 1mg afternoon, and 2mg at evening. Glimpiride (Glorion, Hikma Pharmaceuticals, Amman, Jordan) was used in adaily dose of 4mg before lunch. Patients were followed-up during their visting to AL-Waffa center of diabetes mellitus every 2 weeks to control their compliance with the drug's doses.

Exclusion crieteria includes, patients with severe renal or hepatic impairment whose AST and ALT values were > 3 upper normal limit and serum creatinine greater than 120 mg/ L. , IDDM, pregnant and breast feeding women, patients with known heart diseases such as angina or heart failure, and patients taking other drugs that may affect the outcome of the trial.

Serum glucose concentrations was measured by using enzymatic colorimetric method available as a kit (randox, U.K.). HbA1c was measured by using a commercial kit supplied by STANBIO laboratories, USA.

Statistical Methods: Paired t-test was used to compare the results before and after treatments. Unpaired t-test was used to compare results between treatments. Values were expressed as mean SD and P values of equal and less than 0.05 were considered to be statistically significant.

Results

The number of patients included in this study was 61 type 2 diabetic patients. They are divided into 2 groups, repaglinide group consist of 33 patients (M=23 and F=10). Glimpiride group consist of 28 patients (M=21 and F=7). The 2 groups were matched regarding age (49.15± 7.28 for repaglinide and 52.43± 9.53 years for glimpiride), P >0.1.

Table 1 shows the effects of repaglinide on serum glucose concentrations, HbA1c, and body weight of the diabetic patients. A significant reductions of both FBS and Hba1c were obtained and a significant elevation of body weight was obtained.

Table 2 shows the effects of glimpiride on serum glucose concentrations, HbA1c, and body weight of the diabetic patients. A significant reductions of both FBS and Hba1c were obtained and a significant elevation of body weight was obtained.

Weight elevation after 4 months of treatment with repaglinide or glimpiride were 2.24±2.46 kg and 1.82 ±2.44 kg, respectively. The difference was not significant (P>0.5).

FBS reduction after 4 months of treatment with repaglinide or glimpiride were 75.09±19.18mg/dl and 58.32 ±40.79 mg/dl, respectively. The difference was significant (P<0.05).

HbA1c reduction after 4 months of treatment with repaglinide or glimpiride were 1.77±0.56 % and 1.37 ± 0.76 %, respectively. The difference was significant (P<0.01).

Discussion

This clinical trial demonstrated that both repaglinide and glimpiride had significantly greater reductions of glycemic parameters when used in patients who already had been treated with metformin alone in the previous 3 months. Efficacy differences between the two treatments were evident by the changes in FBS or HbA1c. after therapy. Greater glycemic efficacy of repaglinide was noted by the significant greater reduction of both FBS and HbA1c as compared with the glimpiride group.

With an increasing number of therapeutic choices for oral therapy of type 2 diabetes, the comparative efficacy of various agents and their optimal conditions for use are important considerations. Such comparisons have numerous implications regarding the best therapy to institute in a particular patient populations, including the choice of agents to begin monotherapy when diet and exercise fail or the choice of agents to add to monotherapy to potentiate glucose lowering effects (10).

The efficacy of repaglinide have been evaluated in a number of studies that demonstrated that repaglinide have an antidibetic effects which is similar or better than other antidiabetic agents. In a study that compare the effects of repaglinide with glimpiride in type 2 diabetic patients, repaglinide was found to have therapeutic effects similar to those produced by glimpiride (11).In a another study done by Rosenstock et al (10), repaglinide was found to be more effective than nateglinide monotherapy in reducing HbA1c and FBS after 16 weeks of therapy. Madsbad *et al*, (12) demonstrates that repaglinide is an effective and safe treatment of patients with type 2 diabetes, and is better than glipizide in controlling HbA1c and FBS levels (12).

Glimpiride efficacy have been evaluated in a number of studies. Once daily glimepiride plus diet / exercise was effective in Mexican Americans with type 2 diabetes whose disease was inadequately controlled with diet / exercise alone (13).One study was found that compared adding modified release gliclazide 30-120 mg or glimepiride 1-6 mg daily to current treatment (diet alone, metformin, or acarbose) in 845 patients with type 2 diabetes. HbA1c decreased similarly in both groups from 8.4% to 7.25 on

gliclazide and from 8.2% to 7.2% on glimepiride (14). No significant difference in HbA1c was found at 52 weeks after treatment with glimepiride or glibenclamide. HbA1c was reduced from 8.5± 1.3% at baseline to 8.28± 1.48% for glibenclamide (15).

In this study, it was demonstrated that repiglinide had increased body weight of the patients. Bolen et al. (16) reported that compared with sulfonylureas, repaglinide produce similar gain in body weight (1 to 5 kg). In a study that compared the effect of repaglinide in combination with metformin with monotherapy of each drug on glycemic control in patients with type 2 diabetes, Mosers *et al* (17) reported that an increase in body weight occurred in the repaglinide and combined therapy groups (2.4 +/- 0.5 and 3.0 +/- 0.5 kg, respectively; $P < 0.05$). The results of this articles are in consistent with the results gained in the present study which showed a significant increase in body weight of the diabetic patients treated with repaglinide.

Regarding the effects of glimepiride on body weight, the present study demonstrates a significant increase in body weight of the patients. Our results are in contrast to results obtained by Weitgasser *et al.* (18) who reported that treatment with glimepiride resulted in significant and stable weight loss relative to baseline with the exception of patients with a body mass index of < 25 kg/ m.

In conclusion: The present study showed that both repiglinide and glimperide are effective antidiabetic agents when added to patients who were treated with metformin and have poor glycemic control. The study also demonstrates that repiglinide is significantly reduced both FBS and HbA1c better than glimperide. Both drugs significantly elevate body weight of the patients.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2007; 30 (suppl): S42-S47.
2. Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson MB. Anew look at screening and diagnosing diabetes mellitus. J Clin Endocrinol Metab 2008; 93: 2447-=2453.
3. 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 2003; 26(suppl 1): S5-S20.
4. Agency for Healthcare Research and Quality. Comparative effectiveness and safety of oral diabetes medications for adults with type 2 diabetes. AHRQ available at: http://effectivehealthcare.ahrq.gov

/healthinfo.cfm?infotype=rr&ProcessID=40. July, 2007.

5. Culy CR, Jarvis B. Repaglinide: a review of its therapeutic use in type 2 diabetes mellitus. *Drugs.* 2001;61:1625–1660.

6. Dabrowski M, Wahl P, Holmes WE, Ashcroft FM. Effect of repaglinide on cloned beta cell, cardiac and smooth muscle types of ATP-sensitive potassium channels. Diabetologia 2001;44:747–56.

7. Hatorp V, Oliver S, Su CA. Bioavailability of repaglinide, a novel antidiabetic agent, administered orally in tablet or solution form or intravenously in healthy male volunteers. Int J Clin Pharmacol Ther 1998;36:636–41

8. van Heiningen PN, Hatorp V, Kramer Nielsen K, Hansen KT, van Lier JJ, De Merbel NC, et al. Absorption, metabolism and excretion of a single oral dose of 14C-repaglinide during repaglinide multiple dosing. Eur J Clin Pharmacol 1999;55:521–525.

9. Langtry HD, Balfour JA. Glimepiride. A review of its use in the management of type 2 diabetes mellitus. Drugs 1998; 55: 563-584.

10. Rosenstock J, Hassman DR, Madder RD, Brazinsky SA, Farrell J, Khutoryansky N, et al. Repaglinid versus nateglinide monotherapy. Diabetes Care 2004; 27: 1265-1270.

11. Marbury T, Huang WC, Strange P, Lebovitz H. Repaglinide versus glyburide: a one-year comparison trial. Diabetes Res Clin Pract 1999; 43: 155-166.

12. Madsbad S, Kilhovd B, Lager I, Mustajoki P, Dejgaard A. Comparison between repaglinide and glipizide in type 2 diabetes mellitus: a 1-year multicenter study. Diabet Med 2001; 18: 395-401.

13. Luis Bautista J, Bugos C, Dirnberger G, Atherton T. Efficacy and safety profile of glimepiride in Mexican American patients with type 2 diabetes mellitus: a randomized, placebo-controlled study. Clin Ther 2003; 25:194-209.

14. Schernthaner G, Grimaldi A, DiMario U, Drzewoski J, Kempler P, Kvapil M, et al. Double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. Eur J Clin Invest 2004; 34: 535-542.

15. Dills DG, Schneider J. Clinical evaluation of glimepiride versus glyburide in NIDDM in a double blind comparative study. Horm Metab Res 1996; 28: 426-429.

16. Bolen S, Feldman L, Vassy G, Wilson L, Yeh HC, Marinopoulos S, et. al. Systematic review: comparative effectiveness and safety of oral medications for type 2 dibetes mellitus. Ann Intern Med 2007; 147: 386-399.

17. Moses R, Slobodniuk R, Boyages S, Colagiuri S, Kidson W, Carter J, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control

in patients with type 2 diabetes. Diabetes Care 1999 ;22 :119-24

18. Weitgasser R, Lechleitner M, Luger A, Klingler A. Effects of glimepiride on HbA(1c) and body weight in Type 2 diabetes: results of a 1.5-year follow-up study. Diabetes Res Clin Pract 2003;6:13-19.

Table 1. FBS, HbA1c, and body weight before and after treatment with repaglinide (mean ± s.d.).

Parameter	Before Treatment	After Treatment	P-value
FBS (mg/dl)	171.10±20.97	96.03±14.03	<0.001
HbA1c (%)	8.25±0.60	6.48±0.51	<0.001
Body weight (Kg)	78.52±8.87	80.76±7.59	<0.001

Table 2. FBS, HbA1c, and body weight before and after treatment with glimpiride- (mean ± s.d.).

P-value	After Treatment	Before Treatment	Parameter
<0.001	115.32±22.49	173.64±32.16	FBS (mg/dl)
<0.001	6.91±0.63	8.28±0.55	HbA1c (%)
<0.001	80.00±7.94	78.18±8.66	Body weight (Kg)

الخلاصة:

أجريت هذه الدراسة للمقارنة بين فعالية الريباكلينايد و الكليميبيرايد على المرضى من النوع الثاني لداء السكري.

شملت هذه الدراسة ٦١ مريضا من النوع الثاني لداء السكري يتعالجون بعقار الميتفورمين (٨٥٠ ملغم) يوميا التقييم النهائي للمقارنة بين العقارين اعتمد قياس تركيز السكر في مصل الدم و خضاب الدم المسكر في بداية البحث ثم إعادة قياسهما نهاية مدة الدراسة .

تم إضافة عقار الريباكلينايد الى عقار الميتفورمين وذلك لغرض السيطرة على فرط مستوى السكر في مصل الدم لدى المرضى من النوع الثاني لداء السكري وبجرعة ٥ملغم اجماليا وبواقع ٢ ملغم صباحا ،١ ملغم بعد الظهر و ٢ ملغم مساء وقبل تناول الوجبة . اما بالنسبة لعقار الكليميبيرايد تم اضافته بجرعة ٤ ملغم قبل الغداء . تم قياس تركيز السكر في مصل الدم وخضاب الدم المسكر.