Journal of Food and Drug Analysis, Vol. 11, No. 1, 2003, Pages 1-3 藥物食品分析 第十一卷 第一期

The Effect of Glimepiride on Glycemic Control and Fasting Insulin Levels

TING-TING SEE[1]*, SIU-PAK LEE[2], HUA-FEN CHEN[1] AND HSIN-YU LEE[1]

[1.] Division of Endocrinology and Metabolism, [2.] Division of Neurology, Department of Internal Medicine, Far Eastern Memorial Hospital, 21, Sec 2, Nan Ya South Rd., Panchiao 220, Taipei County, Taiwan, ROC

(Received: June 18, 2002; Accepted: October 24, 2002)

ABSTRACT

Glimepiride is a new once-daily sulfonylurea. Animal studies have shown that it lowers blood glucose through extrapancreatic process. The aim of our study is to observe the effect of glimepiride on glycemic control, body weight change and insulin levels during fasting. Thirty two Type 2 diabetic patients, whose blood glucose levels cannot be controlled adequately with diet and exercise alone, received a 12-week course of glimepiride treatment. They were followed up after 2 weeks, 4 weeks, 8 weeks and 12 weeks. Their fasting, two-hour postprandial blood glucose and body weight were recorded during each visit. Hemoglobulin A1c (HbA1c) and fasting insulin levels were measured at the beginning and end of the study. Fasting plasma glucose (FPG), two-hour postprandial plasma glucose (PPG) and HbA1c values decreased significantly after treatment. The paired mean FPG decreased from 237 ± 66.58 mg/dL to 149 ± 41.31 mg/dL ($P \leq 0.001$), PPG from 352 ± 112.44 mg/dL to 159 ± 22.86 mg/dL ($P \leq 0.001$) and HbA1c from 11.04 ± 2.91% to 6.98 ± 1.52% ($P \leq 0.001$). In contrast, fasting insulin levels and body weight did not have meaningful differences at 0 week and 12 weeks. The paired mean fasting insulin level increased from 13.19 ± 1.52 μIU/mL to 16.76 ± 9.48 μIU/mL ($P = 0.594$). The paired mean body weight increased from 65.01 ± 8.94 kg at baseline to 68.25 ± 9.80 kg at endpoint ($P = 0.023$). Glimepiride lowers blood glucose effectively without much effect on fasting insulin levels and body weight gain. These results suggested that glimepiride lowers blood glucose not only by stimulating insulin secretion but also by its extrapancreatic effects. This metabolic effect is desirable because hyperinsulinemia increases body weight, atherosclerosis and risk of hypoglycemia in diabetic patients.

Key words: glimepiride, fasting insulin level, body weight, glycemic control

INTRODUCTION

Glimepiride is a new sulfonylurea that can be given in a single daily dose. It acts by stimulating insulin release from pancreatic β-cells and possibly via some extrapancreatic mechanisms as well. The major site of activity of glimepiride is thought to be membrane receptors on pancreatic β-cells, where it acts via ATP-regulated potassium (K_{ATP}) channels, resulting in membrane depolarization and release of insulin[(1)]. Direct photoaffinity labeling studies on rat β-cells tumor membrane *in vitro* show that glimepiride binds to 65 kD protein, while other sulfonylureas bind to 140 kD protein[(2)]. Studies in dogs show that a lower ratio of total plasma insulin to total blood glucose occur after oral glimepiride than other sulfonylureas[(3)]. This low ratio suggests that the drug has greater insulin-independent effects on blood glucose than other sulfonylureas. The aim of our study is to observe the effect of glimepiride on glycemic control and fasting insulin levels.

MATERIALS AND METHODS

I. *Materials*

Glimepiride 2 mg tablets (Lot No.40H460) manufactured by Aventis Pharma Co. Ltd. were used.

* Author for correspondence. Tel:886-2-29546200; Fax:886-2-29545567; E-mail:siupakmd@ms1.hinet.net

II. *Patient Population*

Thirty-two Type 2 diabetic patients from the diabetic outpatient clinic of Far Eastern Memorial Hospital participated in the study. Among the participants, there were eighteen male and fourteen female subjects. Their average age was 51.56 ± 12.56 years old. Inclusion criteria included Type 2 diabetic patients whose blood glucose cannot be controlled adequately by diet and physical exercise alone. Grounds for exclusion included: Type 1 diabetes, evidence of hepatic or renal disease, nursing or pregnancy, and suspected allergy to sulfonylureas.

III. *Study Design*

Patients were treated with diet and physical exercise for 2 weeks. Dietary and exercise treatment were considered to be unsuccessful in those with fasting plasma glucose between 151 mg/dL and 300 mg/dL after 2 weeks. The initial dose was 1 mg Glimepiride taken once daily before breakfast. Each patient was followed up for at least 3 months at 2-week, 4-week, 8-week and 12-week intervals. Their fasting and two-hour postprandial blood glucose and body weight were recorded during each visit. Glimepiride was titrated at 1 mg increment until the optimal dose for each patient was obtained. HbA1c and fasting insulin levels were measured at 0 week and 12 weeks. HbA1c is the major form of glycosylated hemoglobin which normally

comprises only 4 – 6% of total hemoglobin. The glycosylation of hemoglobin is dependent on the concentration of blood glucose and the reaction is irreversible. HbA1c generally reflects the state of glycemia over the preceding 8 – 12 weeks. During each visit each patient was inquired about the presence of adverse events, including hypoglycemia, allergic reactions, gastrointestinal upset, headache and other suspected adverse events.

IV. *Assay Method*

Plasma glucose was determined by the hexokinase method (Model 747 Automatic Analyzer, Hitachi, Tokyo, Japan)[4]. HbA1c was done by high performance liquid chromatography affinity columns (CLC385 analyzer Primus corporation, Kansas City, U.S.A.)[5]. Fasting insulin levels were determined by enzyme immunometric assay Immulite (Diagnostic Product Corporation, Los Angeles, U.S.A.)[6]. Laboratory analysis were performed at central laboratory of Far Eastern Memorial Hospital, Taipei, Taiwan. R.O.C..

V. *Statistical Analysis*

The baseline (0 week) fasting insulin level and HbA1c of each patient were compared with endpoint (12 weeks) data using two-tailed paired student's T-test. The paired fasting, two-hour postprandial blood sugar and body weight of each patients recorded at 0 and 12 weeks were compared using ANOVA test. The softwares used for statistical analysis were Excel 2000 and SAS (6.02 edition).

RESULTS AND DISCUSSION

Fasting plasma glucose (FPG), two-hour postprandial plasma glucose (PPG) and HbA1c values decreased significantly after treatment. Average initial glimepiride dose for the whole patient group was 1mg daily. During the observation period the dose was increased to a mean of 3.2 ± 1.1 mg. The clinical efficacy of glimepiride was considered satisfactory if FPG was at 80 mg/dL to 140 mg/dL. The paired mean FPG decreased from 237 ± 66.58 mg/dL to 149 ± 41.31 mg/dL ($P \leq 0.001$), PPG from 352 ± 112.44 mg/dL to 159 ± 22.86 mg/dL ($P \leq 0.001$) and HbA1c from 11.04 ± 2.91% to 6.98 ± 1.52% ($P \leq 0.001$). In contrast, fasting insulin levels and body weight did not have meaningful differences before and after treatment. The paired mean fasting insulin level increased from 13.19 ± 1.52 μIU/mL to 16.76 ± 9.48 μIU/mL ($P = 0.594$). The paired mean body weight increased from 65.01 ± 8.94 kg at baseline to 68.25 ± 9.80 kg at endpoint ($P = 0.023$). (Table 1)

No serious adverse side effects were reported. Two patients complained of dizziness, two had skin rash and one experienced headache. However, these adverse events were tolerable and patients continued with glimepiride treatment.

Glimepiride lowers blood glucose effectively without much effect on fasting insulin levels and body weight.

Table 1. Fasting Plasma Glucose (FPG), Hemoglobin A1c (HbA1c), Two-hour Postprandial Glucose (PPG), Fasting Insulin Level and Body Weight at Baseline and at Endpoint in Patients Receiving Glimepiride

Variable	Baseline	Endpoint	P value
FPG (mg/dL)	237 ± 66.58	149 ± 41.31	≦0.001
HbA1c (%)	11.04 ± 2.91	6.98 ± 1.52	≦0.001
2-hour PPG (mg/dL)	352 ± 112.44	159 ± 22.86	≦0.001
Fasting insulin level (μIU/mL)	13.19 ± 1.52	16.76 ± 9.48	0.594
Body weight (kg)	65.01 ± 8.94	68.25 ± 9.80	0.023

n = 32; values are presented as mean ± SD

These results suggest that glimepiride lowers blood glucose not only by stimulating insulin secretion but also by its extrapancreatic effects. In a euglycemic clamp study, glimepiride increase the rate of metabolic clearance of glucose, demonstrating an increase in insulin activity[7]. The investigators suggest that glimepiride may contribute to overcoming insulin resistance. Several studies explain the mechanisms through which glimepiride facilitated insulin action. *In vitro* glycogenesis and lipogenesis are stimulated by glimepiride in murine 3T3 adipocytes. Glucose transporter 4 (GLUT4) translocation is activated by glimepiride[8]. In rat cardiomyocytes, unlike adipocytes, glimepiride has no acute effect on glucose transport, but increases glucose uptake after chronic exposure, probably through enhancement expression of glucose transporters GLUT1 and GLUT4[9]. The effect of glimepiride on skeletal muscle cell is also studied. It has been found that glimepiride does not alter insulin binding to skeletal muscle insulin receptors in KK-Ay mice[10]. In mice fibroblasts, glimepiride is found to alter glycerol incorporation into diacylglycerol, indicating an effect at an intracellular stage occurring after interactions with the insulin receptor[10].

It has been shown that glimepiride increases two-hour postprandial C-peptide and insulin levels to at least 25% and the absolute change in fasting values is minimal[11]. The risk of exercise-induced hypoglycemia during glimepiride therapy was examined in 167 patients with Type 2 diabetes. Glimepiride is associated with a greater exercise-induced reduction in insulinemia than another sulfonylurea glibenclamide. The investigators suggest that this may reduce the risk of hypoglycemia during exercise[12]. Our study shows that glimepiride lowers blood glucose effectively without much effect on fasting insulin levels and body weight gain. These results can be explained by the extrapancreatic actions of glimepiride. This metabolic effect is desirable because hyperinsulinemia is associated with atherosclerosis, body weight gain and higher risk of hypoglycemia[13].

CONCLUSION

This study demonstrates that glimepiride is a safe and effective oral antidiabetic agent. Patients treated with glimepiride show significantly reduced FPG, HbA1c and 2-

hour PPG. However, fasting insulin levels and body weight do not change significantly. Therefore, with less body weight gain and lower risk of hypoglycemia, glimepiride is a favorable sulfonylurea for Type 2 diabetes who fail to respond to diet and exercise alone.

REFERENCES

1. Kramer, W., Muller, G., Geisen, K. 1996. Characterization of the molecular mode of action of the sulfonylurea, glimepiride, at β-cells. Horm Metab Res 28: 468-4.
2. Kramer, W., Muller, G., Girbig, F. 1994. Differential interaction of glimepiride and glibenclamide with the β-cell sulfonylurea receptor II. Photoaffinity labeling of a 65 kDa protein by [^{3}H] glimepiride. Biochem Biophys Acta 1191: 278-90.
3. Muller, G., Satoh, Y., Geiser, K. 1995. Extrapancreatic effects of sulfonylureas – a comparison between glimepiride and conventional sulfonylureas. Diabetes Res Clin Pract 28 Suppl: S115-37.
4. Okuda, J., Miwa, I., Maeda, K., Tokui, K. 1977. Rapid and sensitive, colorimetric determination of the anomers of D-glucose with D-glucose oxidase, peroxidase, and mutarotase. Carbohydrate Research 58: 267-70.
5. Fairbanks, V. F., Zimmerman, B. R. 1983. Measurement of glycosylated hemoglobin by affinity chromatography. Mayo Clin Proc 58: 770-3.
6. Turkington, R. W., Weindling, H. D. 1978. Insulin secretion in the diagnosis of adult-onset diabetes mellitus. JAMA 240: 833-6.
7. Sato, J., Ohsawa, I., Oshida, Y. 1993. Effects of glimepiride on *in vivo* insulin action in normal and diabetic rats. Diabetes Res Clin Pract 22: 3-9.
8. Muller, G., Wied, S., Wetekan, E. M. 1994. Stimulation of glucose utilization in 3T3 adipocytes and rat diaphragm *in vitro* by the sulfonylureas, glimepiride and glibenclamide, is correlated with modulations of the cAMP regulatory cascade. Biochem Pharmacol 48: 985-96.
9. Eckel, J. 1996. Direct effects of glimepiride on protein expression of cardiac glucose transporters. Horm Metab Res 28: 508-11.
10. Takada, Y., Takata, Y., Iwanishi, M. 1996. Effect of glimepiride on insulin receptors of skeletal muscles from genetically diabetic KK-Ay mouse. Eur J Pharmacol 308: 205-10.
11. Rosenstock, J., Samols, E., Muchmore, D.B. 1996. Glimepiride, a new once-daily sulfonylurea: a double-blind placebo-controlled study of NIDDM patients. Diabetes Care 19: 1194-9.
12. Massi-Benedetti, M., Herz, M., Pfeiffer, C. 1996. The effects of acute exercise on metabolic control in type 2 diabetic patients treated with glimepiride or glibenclamide. Horm Metab Res 28: 451-5.
13. Stolar, M. W. 1988. Atherosclerosis in diabetes: the role of hyperinsulinemia. Metabolism 37(suppl 1): 1-9.