Glimepiride in Type 2 Diabetes Mellitus Thai Patients

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Abstract

This study aimed to confirm the efficacy of glimepiride given once daily in the treatment of Thai type 2 diabetic patients and to find out the optimum dosage for Thai patients. The patients were enrolled at the diabetic clinics of 5 hospitals (Rajavithi, Chulalongkorn, Pramongkutklao, Siriraj and Theptarin Hospitals). All patients started glimepiride 1 mg once daily and escalated to 2, 3, 4 and until 6 mg every 4 weeks if fasting plasma glucose (FPG) exceeded 140 mg/dL. Subjects were 60 females and 29 males with an average age of 52.2 $\pm$ 10.0 years. Mean BMI was 25.5 $\pm$ 3.8 kg/m^2. Fifty seven patients (64.0%) were drug naïve and thirty two patients (36.0%) had been previously treated with oral hypoglycemic agents. Seventy three per cent of the drug naïve and 37 per cent of the previously treated patients could be controlled with 1-2 mg of glimepiride once daily. At the twelfth week of treatment, mean fasting plasma glucose decreased from 224.6 to 156.6 mg/dL (30% reduction) and mean HbA_{1c} decreased from 10.0 to 7.5 per cent (25% reduction). At the end of the study 49.4 per cent of the patients had HbA_{1c} < 7.0 per cent, 21.3 per cent had HbA_{1c} 7.0-8.0 per cent and 29.3 per cent had HbA_{1c} > 8.0 per cent. Adverse events that were probably or possibly related to the drug were reported in 5 patients (5.6%). Three of them were hypoglycemia and two patients had skin rash. All hypoglycemic episodes were mild. Glimepiride was indicated to be safe. There were no clinically significant changes in clinical laboratory values, physical examinations and vital signs. In conclusion, glimepiride was efficacious and safe in type 2 diabetes Thai patients and 1-2 mg of glimepiride appeared to be a sufficient dose for most newly diagnosed type 2 diabetic patients.

Key word : Type 2 Diabetes, Glimepiride, Sulfonylurea, Treatment

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Glimepiride, a new sulfonylurea, lowered blood glucose by stimulating insulin release from the pancreas[1] and also appeared to have extra-pancreatic effects[2-4]. Glimepiride has been shown to be effective and well-tolerated from the range of 1-8 mg once daily in type 2 diabetic Caucasian patients[5,6]. Double blind comparative studies showed that glimepiride had equivalent metabolic control as glibencamide but fewer hypoglycemic reactions[7,8]. Studies in humans showed that glimepiride was associated with fewer direct effects on the ATP-sensitive K+channels of the cardiovascular system than glibenclamide[9,10]. The objective of this study was to assess the efficacy and safety of glimepiride in type 2 diabetic Thai patients and to find out the optimum dosage for Thai patients.

MATERIAL AND METHOD

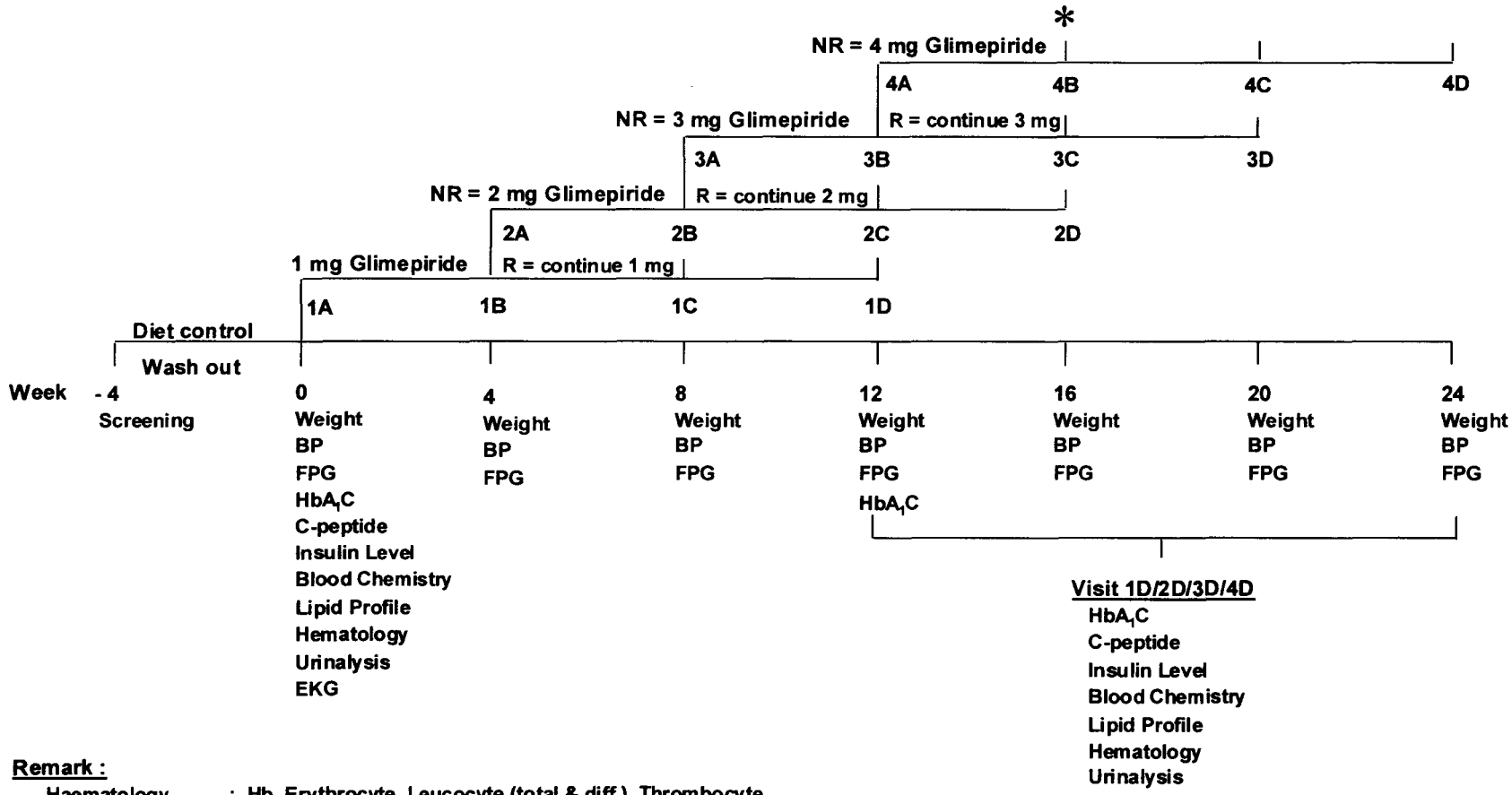
Patients with type 2 diabetes mellitus were recruited from the outpatient diabetic clinics of 5 centers including Rajavithi Hospital, King Chulalongkorn Memorial Hospital, Pramongkutklao Hospital, Siriraj Hospital and Theptarin Hospital. The inclusion criteria were: patients with type 2 diabetes mellitus aged between 35 and 75 years, either drug naïve or previously treated with oral hypoglycemic agents that had been stopped for at least 4 weeks, fasting plasma glucose (FPG) between 180-300 mg/dl and BMI 20-40 kg/m^2. The exclusion criteria were: history of hypersensitivity to sulfonylureas, patients requiring insulin treatment, history of using concurrent therapy during the last 4 weeks which may affect glucose tolerance eg. corticosterioids, pregnant or breast feeding women, SGOT or SGPT values greater than 2 times the upper normal limit and serum creatinine greater than 1.5 mg/dl.

Schedule of the visits is shown in Fig. 1. Before starting the study medication, patients had started dietary control or stopped oral antidiabetic drugs for 4 weeks (wash out period). The first dose of glimepiride 1mg was taken on the day of the first visit (week 0). This dosage was continued for 4 weeks, then the patients returned to the clinic for physical and laboratory evaluation (week 4). The patients were considered to be responders if FPG $\leq$ 140 mg/dl and the same dose was continued and further evaluation was performed at a 4-weekly interval until completing 12 weeks (visits 1C and 1D-last visit). If the patient was a non-responder (FPG > 140 mg/dl), the dose was increased to 2 mg/day and he/she started the new dose on the day of the visit. Further evaluation for this patient was done after 4 weeks (visit 2B) and the patient was evaluated as to whether he/she was a responder or non-responder. Responders remained on the same dosage and further evaluation was performed at a 4-weekly interval until completing 12 weeks (visits 2C and 2D-last visit). Non-responders increased the dose to 3 mg/day starting on the visit day, with the next evaluation after 4 weeks (visit 3B). Responders to this dosage continued and were evaluated at 4-weekly intervals (visits 3C and 3D-last visit), while non-responders increased the dose to 4 mg/day and the next evaluation was done after 4 weeks (visit 4B). Responders remained on the same dosage until further evaluation after 4-weekly intervals (visit 4C and 4D-last visit), while non-responders increased the dose to 6 mg/day or changed to other antidiabetic drugs. Physical examination including weight, height, blood pressure measurement and fasting plasma glucose was done at every visit. Blood for complete blood count, lipid profiles, HbA_{1c}, insulin, C-peptide and chemistry (SGOT, SGPT, alkaline phosphatase, total protein, albumin, BUN, creatinine, uric acid) was taken at visit 0 and visit1D/2D/3D/4D.

Plasma glucose was determined by the glucose oxidase method. HbA_{1c} was measured by the HPLC method (BIO-RAD, USA; normal range 4.1-6.5%). Serum insulin and C-peptide were measured by the RIA method. Lipid profiles were done by enzymatic methods. All data were expressed as the mean $\pm$ SD. Statistical analysis was performed by paired *t*-test, unpaired *t*-test and Wilcoxon's signed rank test. P values < 0.05 were considered to be statistically significant. The statistical package SPSS for windows was used for all the analysis.

RESULTS

One hundred and four type 2 diabetic patients were enrolled in this study. Fifteen patients were excluded from the study due to protocol violation, so eighty nine patients were evaluated in this study. During the study, 6 patients were lost to follow-up and 8 patients were withdrawn from the study. The efficacy analyses were based on the 75 patients who completed the study and safety analysis was based on 89 patients. Table 1 shows the clinical characteristics of the patients. There were 64 per cent drug naïve patients and 36 per cent previously treated with oral hypoglycemic agents. Most common antidiabetic drugs were sulfonylurea



Remark :

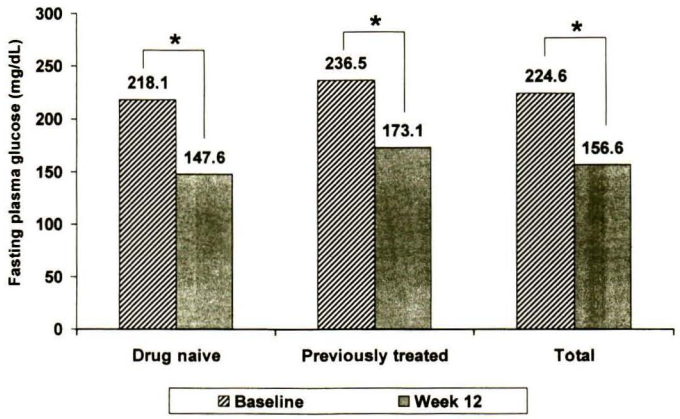
Haematology	: Hb, Erythrocyte, Leucocyte (total & diff.), Thrombocyte
Lipid profile	: Triglyceride, Cholesterol, LDL, HDL
Blood Chemistry	: SGPT, SGOT, Alkaline Phosphatase, Total protein, Albumin, BUN, Creatinine, Uric acid
Urinalysis	: pH, Albumin, Glucose, RBC, WBC, Microscopic exam. (bacteria, casts)
R	: Responder FPG $\leq$ 140 mg/dl
NR	: Non Responder
*	: escalate dose in Non Responder up to 6 mg/day or add or change to other antidiabetic drugs.

Fig. 1. Schedule and dose escalation flow chart of glimepiride study.

Table 1. Clinical characteristics of the 89 type 2 diabetic patients.

	Total (n=89)	Drug naïve (n=57)	Previously treated (n=32)
Gender (male : female)	29 : 60	22 : 35	7 : 25
Age (years)	52.2 ± 10.0	51.9 ± 9.3	52.8 ± 11.3
BMI (kg/m^2)	25.5 ± 3.8	25.9 ± 4.2	24.7 ± 3.1
Fasting plasma glucose (mg/dl)	224.6 ± 47.2	214.8 ± 48.4	237.9 ± 41.4
HbA_{1c} (%)	10.0 ± 2.1	10.2 ± 2.1	9.6 ± 2.0
Serum insulin (μU/ml)	12.0 ± 14.7	12.8 ± 17.8	10.4 ± 6.0
C-peptide (ng/ml)	1.8 ± 0.6	2.1 ± 0.6	1.2 ± 0.4

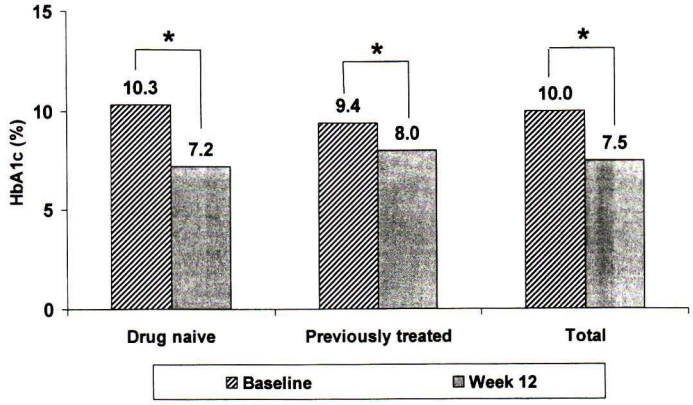
Data are shown as number or mean ± SD



*P-value < 0.0001

Fig. 2. Effect of 12-week treatment with glimepiride on mean fasting plasma glucose.

(84.4%) and metformin (9.4%). At baseline 87.6 per cent of the patients did not have any diabetes related complications. Diabetic retinopathy, nephropathy and neuropathy were detected in 4.5 per cent, 5.6 per cent and 2.2 per cent respectively. After 12-weeks of treatment with glimepiride 1 mg/day fasting plasma glucose and HbA_{1c} decreased from baseline 30.3 per cent and 25.0 per cent respectively as shown in Fig. 2 and 3. At the end of the study, 31 patients continued glimepiride 1 mg/day for 12 weeks. Fourteen patients and four patients were escalated and continued glimepiride 2 and 3 mg/day respectively. Twenty six cases were escalated and continued glimepiride 4-6 mg/day until the end of the study. The percentage of the patients who were responders at each dosage of glimepiride compared between the drug naïve patients and these previously treated with oral hypoglycemic drugs is shown in Fig. 4. The majority (52.1%) of drug naïve type 2 diabetic patients responded to 1 mg/day of glimepiride while 55.6 per cent of the previously treated patients required 4-6 mg/day. Fasting plasma glucose and HbA_{1c} at each visit of the patients who were on each dose of glimepiride are shown in Fig. 5 and 6. At the end of the study, 49.4 per cent of the patients had HbA_{1c} < 7.0 per cent, 21.3 per cent had HbA_{1c} 7.0-8.0 per cent and 29.3 per cent had HbA_{1c} > 8.0 per cent. Changes in serum insulin and C-peptide level were not statistically significant after treatment except for the subgroup of 1 mg glimepiride responders who had significantly increased serum insulin (9.1±5.4 to 12.7±6.1 mU/ml, p-value = 0.002) and C-peptide (1.7±0.7 to 2.1±0.9 ng/ml, p-value = 0.029) after treatment. Changes in serum chemistry and lipid profiles were not statistically significant after treatment.



*P-value < 0.0001

Fig. 3. Effect of 12-week treatment with glimepiride on mean HbA_{1c}.

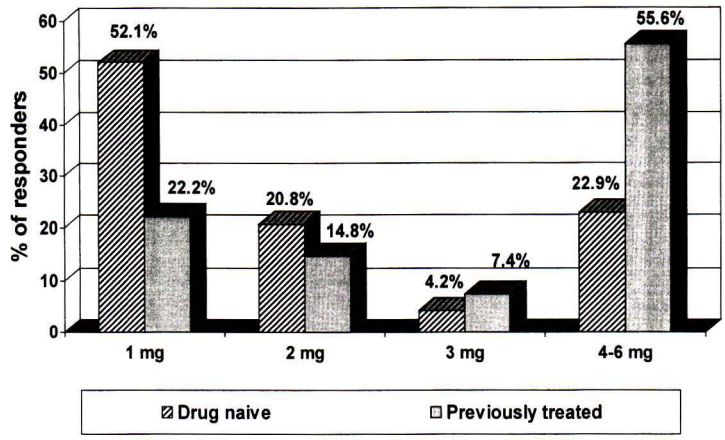
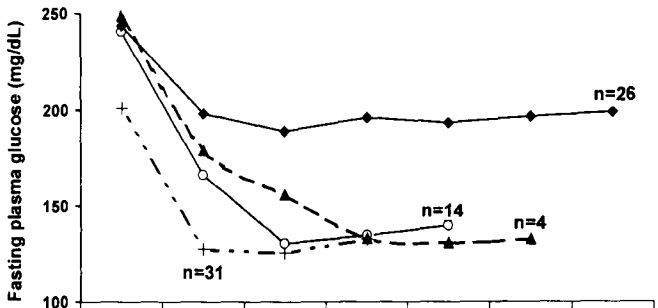


Fig. 4. Percentage of responders at each dosage of glimepiride.

Adverse events that were probable or possibly related to the drug were reported in 5 patients (5.6%). Three patients reported hypoglycemia and two patients had skin rash. All of the hypoglycemic events were mild.

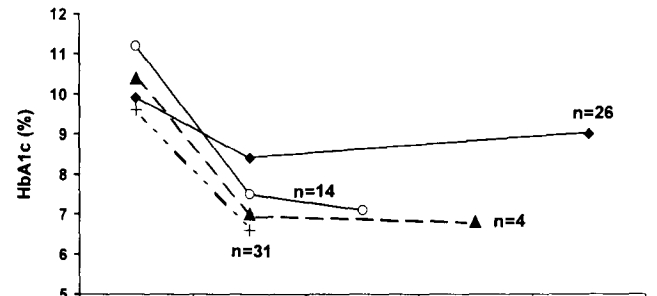
DISCUSSION

This study confirms that glimepiride is a potent oral hypoglycemic agent at once-daily doses in type 2 diabetic patients. Most of the drug naïve type 2 diabetic Thai patients responded to 1-2 mg/day of glimepiride while the previously treated patients needed higher doses. Most of the previously treated patients who had used other sulfonylureas before entering the study meant that their beta cell functions were impaired more than the drug naïve patients. This was confirmed by the data of our baseline fasting C-peptide that was higher in the drug naïve group (2.1 ± 0.6 *vs* 1.2 ± 0.4 ng/ml, p-value <0.01). There was no significantly difference in the baseline fasting plasma glucose or HbA_{1c} compared between the patients who responded to 1, 2, 3 mg or a higher dosage of glimepiride. Most of the patients who increased the dosage of glimepiride to 4 mg or higher did not achieve good glycemic control (fasting plasma glucose > 140 mg/dl and HbA_{1c} > 7.0%) at the end of the study. This implies that when patients are inadequately glycemic controlled



	Wk0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24
1 mg	201.1	127.2	125.6	132.3			
2 mg	240.1	166.0	130.2	134.0	139.4		
3 mg	248.5	179.5	156.0	132.8	130.5	132.3	
4-6 mg	243.7	198.5	189.0	196.0	193.4	196.5	198.8

Fig. 5. Mean fasting plasma glucose at each visit of the patients taking different dosage of glimepiride.



	Wk0	Wk12	Wk16	Wk20	Wk24
1 mg	9.6	6.6			
2 mg	11.2	7.5	7.1		
3 mg	10.4	7.0		6.8	
4-6 mg	9.9	8.4			9.0

Fig. 6. Changes of mean HbA_{1c} in the patients taking different dosage of glimepiride.

with glimepiride of more than 3 mg/day, instead of increasing the dose of glimepiride, we should add another group of oral hypoglycemic agents that have a different action such as insulin sensitizers that improve insulin action without stimultating insulin secretion. The HbA_{1c} reduction by glimepiride in this study is quite high (25%; 10.0% to 7.5%) when compared with other studies[5,6,11]. This may explain that the predominate defect in the pathogenesis of type 2 diabetes in the Thai population is insulin secretory function while insulin resistance is the major defect in Caucasians. About seventy five per cent of type 2 diabetic Caucasian patients were obese[12] while only half of type 2 diabetic Thai patients were obese[13]. This finding is consistent with the present study that the mean BMI of our patients was 25.5 kg/m^2 and 51.2 per cent had BMI $\geq$ 25 kg/m^2.

Glimepiride in type 2 diabetic Thai patients appears to be safe and well tolerated. There was no evidence of serious adverse events that could possibly be related to the drug in the current study. The treatment-related complications were mild hypoglycemia and skin rashes.

Treatment compliance is one of the most common problems among type 2 diabetic patients [14,15]. Pullar et al[16] reported that compliance was best among type 2 diabetic patients randomized

to take a once-daily treatment regimen compared with more frequent dosing. Although not specifically addressed in the current study, the ability to administer glimepiride once daily may improve treatment compliance.

In conclusion, the results of the current study indicate that glimepiride is a safe and effective oral hypoglycemic agent for the treatment of type 2 diabetes mellitus Thai patients. Most type 2 Thai diabetic patients who did not achieve glycemic control after medical nutritional therapy responded well to glimepiride 1-2 mg once daily.

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REFERENCES

1. Leclercq-Meyer V, Akkan AG, Marchand J, Malaisse WJ. Effects of glimepiride and glibencamide on insulin and glucagon secretion by the perfused rat pancreas. Biochem Pharmacol 1991; 42: 1634-7.
2. Sato J, Ohsawa I, Oshida Y, Sato Y, Sakamato N. Effects of glimepiride on *in vivo* insulin action in normal and diabetic rats. Diabetes Res Clin Pract 1993; 22: 3-9.
3. Muller G, Wied S. The sulfonylurea drug, glimepiride, stimulates glucose transport, glucose transporter translocation, and dephosphorylation in insulin-resistant rat adipocytes *in vitro*. Diabetes 1993; 42: 1852-67.
4. Bahr M, von Holtey M, Muller G, Eckel J. Direct stimulation of myocardial glucose transport and glucose transporter-1 (GLUT1) and GLUT4 protein expression by the sulfonylurea glimepiride. Endocrinology 1995; 136: 2547-53.
5. Goldberg RB, Holvey SM, Schneider J. A dose-response study of glimepiride in patients with NIDDM who have previously received sulfonylurea agents. Diabetes Care 1996; 19: 849-56.
6. Rosenstock J, Samols E, Muchmore DB, Schneider J. Glimepiride, a new once-daily sulfonylurea. Diabetes Care 1996; 19: 1194-9.
7. Draeger KR, Wernicke-Panten K, Lomp HJ, Schuler E, Rosskamp R. Long-term treatment of type 2 diabetic patients with the new oral antidiabetic agent glimepiride: A double-blind comparison with glibencamide. Horm Metab Res 1996; 28: 419-25.
8. Dills DG, Schneider J. Clinical evaluation of glimepiride *versus* glyburide in NIDDM in a double-blind comparative study. Horm Metab Res 1996; 28: 426-9.
9. Bijlstra PJ, Lutterman JA, Russel FG, Thien T, Smits P. Blockade of vascular ATP-sensitive potassium channels reduces the vasodilator response to ischaemia in humans. Diabetologia 1996; 39: 1562-8.
10. Klepzig H, Kober G, Matter C, et al. Sulfonylureas and ischaemic preconditioning: A double-blind, placebo-controlled evaluation of glimepiride and glibencamide. Eur Heart J 1999; 20: 439-46.
11. Hariharan RS, Nihalani KD, Sahay BK, Seshiah V, Vakil HB, Venkataraman S. A multicenter study of the efficacy and tolerability of glimepiride in Indian Patients with type 2 diabetes mellitus. The J Gen Med 1999; 11: 69-75.
12. Lean MEJ, Powrie JK, Anderson AS, Garthwaite PH. Obesity, weight loss and prognosis in NIDDM. Diabetic Med 1990; 7: 3228-33.
13. Thai Multicenter Research Group on Diabetes Mellitus. Comparison of non-insulin dependent diabetics in four regions of Thailand. Int Med 1994; 10: 27-33.
14. Kurtz SMS. Adherence to diabetes regimens: Empirical status and clinical applications. Diabetes Educ 1990; 16: 50-6.
15. Nagasawa M, Smith MC, Barnes JH, Fincham JE. Meta-analysis of correlates of diabetes patients' compliance with prescribed medications. Diabetes Educ 1990; 16: 192-200.
16. Pullar T, Birtwell AJ, Wiles PG, Hay A, Feely MP. Use of a pharmacologic indicator to compare compliance with tablets prescribed to be taken once, twice, or three times daily. Clin Pharmacol Ther 1988; 44: 540-5.

การศึกษาประสิทธิภาพและความปลอดภัยของการใช้ยากลัยเมพิไรด์ในการรักษาผู้ป่วยไทยที่เป็นโรคเบาหวานชนิดที่ 2

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การศึกษานี้มีวัตถุประสงค์เพื่อดูประสิทธิภาพและความปลอดภัยของการใช้ยากลัยเมพิไรด์ในการรักษาผู้ป่วยเบาหวานชนิดที่ 2 ในคนไทย โดยทำการศึกษาผู้ป่วยในคลินิกโรคเบาหวานของโรงพยาบาลราชวิถี จุฬาลงกรณ์ พระมงกุฎเกล้า ศิริราช และเทพธารินทร์ ผู้ป่วยจะได้รับยากลัยเมพิไรด์ขนาด 1 มิลลิกรัมต่อวัน และขนาดยาเพิ่มเป็น 2, 3, 4 และ 6 มิลลิกรัม ทุก 4 สัปดาห์ หากระดับน้ำตาลในเลือดขณะอดอาหารมีค่ามากกว่า 140 มก/ดล. ผู้ป่วยเบาหวานจำนวน 89 ราย ได้รับคัดเลือกในการศึกษานี้ อายุเฉลี่ย 52.2 ± 10.0 ปี ดัชนีมวลร่างกายเฉลี่ย 25.5 ± 3.8 กิโลกรัม/เมตร^2 ร้อยละ 64 ของผู้ป่วยไม่เคยได้รับยาลดระดับน้ำตาลในเลือดมาก่อน ผลการศึกษาพบว่าร้อยละ 73 ของผู้ป่วยเบาหวานที่ไม่เคยได้รับยาลดระดับน้ำตาลในเลือดมาก่อนและร้อยละ 37 ของผู้ป่วยเบาหวานที่เคยได้รับยาลดระดับน้ำตาลในเลือดมาก่อนสามารถควบคุมระดับน้ำตาลในเลือดได้อย่างดีด้วยยากลัยเมพิไรด์ขนาด 1–2 มก.ต่อวัน หลังการรักษา 12 สัปดาห์ค่าเฉลี่ยของระดับน้ำตาลในเลือดขณะอดอาหารลดลงจาก 224.6 เป็น 156.6 มก/ดล. (ลดลงร้อยละ 30) ค่าเฉลี่ยของฮีโมโกลบินเอวันซีลดลงจากร้อยละ 10.0 เป็น 7.5 (ลดลงร้อยละ 25) เมื่อสิ้นสุดการศึกษาร้อยละ 49.4 ของผู้ป่วยเบาหวานมีระดับฮีโมโกลบินเอวันซีน้อยกว่าร้อยละ 7 ร้อยละ 21.3 ของผู้ป่วยมีระดับฮีโมโกลบินเอวันซีระหว่าง 7.0–8.0 และร้อยละ 29.3 ของผู้ป่วยมีระดับฮีโมโกลบินเอวันซีมากกว่าร้อยละ 8 อาการข้างเคียงของยาพบในผู้ป่วย 5 ราย (ร้อยละ 5.6) ผู้ป่วย 3 รายมีอาการของระดับน้ำตาลในเลือดต่ำไม่รุนแรงและผู้ป่วย 2 รายมีผื่นผิวหนัง ผลการตรวจเลือดทางชีวเคมีอื่น ๆ ไม่พบมีการเปลี่ยนแปลงหลังการรักษาอย่างมีนัยสำคัญทางสถิติ โดยสรุปยากลัยเมพิไรด์มีประสิทธิภาพดีและปลอดภัยในการรักษาผู้ป่วยเบาหวานชนิดที่ 2 ในคนไทยและยากลัยเมพิไรด์ขนาด 1–2 มก/วัน เป็นขนาดที่เหมาะสมและเพียงพอในการรักษาผู้ป่วยเบาหวานชนิดที่ 2 ส่วนใหญ่ที่ไม่สามารถควบคุมระดับน้ำตาลในเลือดได้ดีหลังจากการควบคุมอาหารและการออกกำลังกาย

คำสำคัญ : โรคเบาหวานชนิดที่ 2, ยากลัยเมพิไรด์, ซัลโฟนิลยูเรีย, การรักษา

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