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Double-blind, randomized, multicentre study of the efficacy and safety of gliclazide-modified release in the treatment of Chinese type 2 diabetic patients

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Background and Aim: Gliclazide-modified release (gliclazide MR) is a new formulation of the sulfonylurea gliclazide designed for once-daily administration. The hydrophilic matrix of hypromellose-based polymer in the new formulation induces a progressive drug release, which parallels the 24-h glycaemic profile in type 2 diabetic patients. The aim of this study was to compare the efficacy and safety of gliclazide MR (once-daily administration) versus gliclazide (twice-daily administration) in Chinese type 2 diabetic patients.

Materials and Methods: Sixty-three type 2 diabetic Chinese patients who had been on diet control alone or on treatment with metformin or on low dose of sulfonylurea were randomized to either gliclazide MR taken once daily or gliclazide taken twice daily. Dosage of metformin was maintained throughout the study, and the sulfonylurea was stopped. The dose of gliclazide MR was increased at 1-month intervals from 30 mg to 120 mg, while that of gliclazide from 80 mg to 320 mg until metabolic control was achieved [fasting plasma glucose (FPG) $\leq$7.7 mmol/l] or the maximum dose reached. Efficacy was mainly evaluated by levels of haemoglobin A1c (HbA1c) and FPG.

Results: The mean baseline characteristics of the full analysis set 1 (FAS1) (HbA1c, n = 58) and the FAS2 (FPG, n = 61) were comparable in both groups. The levels of HbA1c decreased similarly in both groups over the treatment period: $-1.6 \pm 1.6\%$ ($p < 0.001$) on gliclazide MR (n = 31) and $-1.6 \pm 1.4\%$ ($p < 0.001$) on gliclazide (n = 27). Decrease in HbA1c was observed irrespective of pre-existing therapy for diabetes: $-2.3 \pm 1.5\%$ for patients on diet alone; $-0.6 \pm 1.3\%$ for patients switched from sulfonylurea to study drug and $-1.4 \pm 0.8\%$ for patients on metformin in combination with study drug. FPG decreased significantly from 177.5 ± 63.5 to 136.7 ± 42.2 ($p < 0.001$, n = 32) on gliclazide MR and not significant from 188.2 ± 62.6 to 163.7 ± 67.9 ($p = 0.059$, n = 29) on gliclazide. Both treatments were very well tolerated with no major hypoglycaemic episodes requiring external assistance; only three patients experienced mild hypoglycaemic episodes.

Conclusions: Once-daily gliclazide MR showed a better trend in improving blood glucose control in comparison with gliclazide in type 2 diabetic Chinese patients irrespective of the pre-existing anti-diabetic treatment. The safety profiles of gliclazide MR and gliclazide were similar with a small number of patients having reported hypoglycaemic episodes. Once-daily dosing with gliclazide MR should improve patient compliance, an important factor in long-term glycaemic control.

Keywords: Chinese type 2 diabetic patients, gliclazide, new formulation, sulfonylurea
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Introduction

Type 2 diabetes is the most common form of diabetes mellitus, accounting for approximately 90% of cases and affecting about 100 million people in the world. Projections indicate that there will be over 215 million type 2 diabetic patients by the year 2010 [1]. Over time, diabetes can lead to blindness, kidney failure and nerve damage. Diabetes is also an important factor in accelerating atherosclerosis, leading to cerebrovascular disease, coronary heart disease and peripheral vascular disease. These complications may result in increasing disability, reduce life expectancy and entail enormous health cost to society [2–4]; diabetes is amongst the fifth leading cause of death by disease in most countries. Therefore, diabetes is certainly one of the most challenging health problems in the 21st century.

Type 2 diabetes is a metabolic disorder caused by a combination of insulin secretion alteration and decreased insulin action resulting in chronic hyperglycaemia [5]. Sulfonylureas are potent hypoglycaemic agents acting mainly through their insulin secretory capacity [6]. Gliclazide is a second-generation sulfonylurea. It works in several different ways, but its primary function is to increase insulin sensitivity and acts against both platelet adhesiveness and aggregation and oxidative stress [7], all recognized elements in the pathogenesis of diabetes vascular diseases [8–10]. Since its introduction in 1972, gliclazide is currently registered in more than 120 countries and is indicated in the treatment of the adult and elderly type 2 diabetes without ketoacidosis when diet control fails to achieve a good glycaemic control.

Gliclazide-modified release (Gliclazide MR) is a new pharmaceutical formulation of gliclazide with modified-release characteristics. Compared with the current formulation, it offers a more predictable release of the active principle and allows for once-daily administration. A double-blind, randomized multicentre study including a total of 800 patients in 11 countries has shown that gliclazide MR is at least as efficacious as gliclazide in controlling haemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) in type 2 diabetic patients and a lower daily dose of gliclazide MR (30–120 mg) than that of gliclazide (80–320 mg) [11]. In the subset of type 2 diabetic patients previously on diet only, gliclazide MR induced a marked improvement of HbA1c and FPG levels. The safety profile of gliclazide MR is similar to that of gliclazide; gliclazide MR did not lead to more frequent hypoglycaemic episodes.

This study aimed to confirm that gliclazide MR achieves a similar improvement of blood glucose control than the current gliclazide formulation for the treatment of type 2 diabetic patients on diet control alone or on diet control and anti-diabetic monotherapy (α-glucosidase inhibitor or biguanide or low dose of sulfonylurea) in Taiwan.

Materials and Methods

This was a double-blind, comparative, randomized multicentre study conducted in type 2 diabetic patients (figure 1). The patients were eligible to enter the run-in period of the study if they fulfilled the following criteria: male or female outpatients aged from 30 to 75 years with body mass index (BMI) ranging from 21 to 35 kg/m^2 with type 2 diabetes known for at least 3 months (treated with diet for ≥3 months, or with diet and α-glucosidase inhibitor or with diet and biguanide for ≥3 months at a constant dosage, or with diet and a low dose of sulfonylurea for ≥3 months at a constant dosage before selection, such as ≤80 mg of gliclazide, ≤1 mg glimepiride, ≤5 mg glibenclamide or ≤5 mg glipizide), having HbA1c values ≥7% obtained within 1 month before study entry, with ability to comply with the protocol and to cooperate during the study, having given their written informed consent to participate and efficient contraception for female patients with child-bearing potential.

The exclusion criteria were type 1 diabetes, type 2 diabetes treated with insulin in the previous 3 months before selection, diabetes linked to chronic pancreatitis, genetic defects of β-cell function, genetic defects in

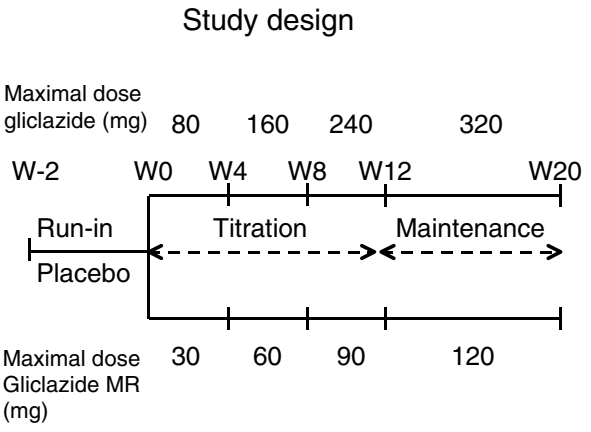

Fig. 1 A double-blind, comparative, randomized multicentre study conducted in Chinese type 2 diabetic patients.

insulin action-like lipoatrophic diabetes, haemochromatosis, endocrinopathies, poorly controlled diabetes owing to an intercurrent illness, infection or surgery, ketosis or ketoacidosis, history of allergy to sulfonamides, drugs contraindicated with biguanide or a-glucosidase inhibitor (for patients treated with α-glucosidase inhibitor or biguanide), concomitant treatments affecting glucose metabolism or gliclazide metabolism, conditions related to concomitant diseases such as acute and chronic conditions apart from diabetes, which could have precluded end-point evaluation or progress in the study, for example all factors or diseases interfering with HbA1c analysis (serious anaemia, haemoglobinopathy, haemolysis and blood clotting), endocrine diseases other than diabetes, immunosuppression, surgical procedures, either recent or planned during the study, pregnancy or lactation, abuse of drug or alcohol, participation in another study in the previous 2 months, serum creatinine >1.7 mg/dl, aminotransferase or alkaline phosphatase greater than threefold upper normal range and uncooperative or unreliable patients.

After selection (week-2 visit), the patients entered in a 2-week single blind run-in period on placebo. Patients on a-glucosidase inhibitor or biguanide or low dose of sulfonylurea were asked to continue their usual treatment without changing the dose in combination with the placebo, and dietary advice were reinforced. The patients to be included should have had compliance greater than 80% and lower than 120% at the end of the 2-week run-in period.

At week-0 visit, the patients were randomized on either gliclazide MR or gliclazide for 20 weeks. Treatments were allocated by balanced randomization in each centre without any stratification. The randomization list was designed by the Biometric Department of I.R.I.S and constructed by the Clinical Supply Unit, Gidy (France). Patients on α-glucosidase inhibitor or biguanide continued their treatment without changing the dose all over the study duration. α-Glucosidase inhibitor or biguanide was thus associated to the randomized study treatment. Patients on low dose of sulfonylurea were asked to stop their treatment during the randomized study period (from week-0 to week-20 visits) and were switched to the randomized study treatment.

From week-0 visit to week-12 visit, the patients entered in a 12-week therapeutic adjustment period (titration period). Patients started with the lowest dose (i.e. gliclazide 80 mg or gliclazide MR 30 mg), and the dosage was then gradually increased at every 4-week visit to achieve an optimal glycaemic control (FPG ≤7.7 mmol/l or the maximum dose reached). At the end of the titration period (week-12 visit), patients continued for an 8-week maintenance period during which the dosage was maintained unchanged. Whatever the treatment and the dosage to which the patients were allocated, the patients took four capsules daily: two capsules each morning before breakfast and two capsules each evening before dinner. Capsules were to be ingested with 100 ml of drinking water.

Efficacy was measured by HbA1c, which would be centrally assessed in the laboratory of NTUH Hospital at week-0, week-12 and week-20 visits. FPG was centrally assessed in the laboratory of NTUH Hospital at week-0, week-4, week-8, week-12 and week-20 visits. Weight, BMI, blood pressure and heart rate were recorded at each study visit. Haematology, biochemistry (sodium, potassium, serum creatinine, alkaline phosphatase, aminotransferase and total proteins) and lipids (total cholesterol, high-density lipoprotein cholesterol, low density lipoprotein-cholesterol and triglyceride) were centrally assessed in the laboratory of NTUH Hospital at week-0 and week-20 visits.

Serious adverse events were defined as events resulting in death, persistent or significant disability or incapacity, hospitalization or prolongation of pre-existing hospitalization, severe hypoglycaemia and life-threatening events. Acute intoxication, important medical events and pregnancy were to be considered as serious events.

Descriptive statistics, such as number of observations, mean, standard deviation, median, minimum, maximum and 95% confidence interval, were used to summarize the continuous variables. Frequency and proportion were used to summarize the categorical variables. All available data were displayed by treatment groups and overall. For efficacy analysis, the hypothesis of interest is to detect a difference in the gliclazide MR group in evolution from baseline of HbA1c. All statistical tests were two-sided and interpreted at the 5% level of significance. The analysis of main efficacy criteria was based on full analysis set 1 (FAS1) for HbA1c and on FAS2 for FPG. Time limits between two consecutive visits and total duration of treatment were determined. Compliance at each visit as well as during titration and maintenance periods was described. Status of patients and reason for withdrawal were described. No imputation was done for estimating the missing value.

In FAS1 and FAS2, change over time from baseline (week-0) to last measurement under treatment on efficacy criteria were analysed separately in each group, using a two-tailed Student's *t*-test for paired

Table 1 Baseline characteristics of the 63 patients randomized to receive gliclazide-modified release (gliclazide MR) or gliclazide

Baseline characteristics	Gliclazide MR (n = 32)	Gliclazide (n = 31)
Mean age (±SD) (years)	54.8 ± 11.0	56.2 ± 9.2
Male (%)	59	65
Mean duration of the diabetes (±SD*) (m)	29.0 ± 20.0	28.9 ± 29.5
Family history of diabetes (%)	31	23
Mean weight (±SD) (kg)	67.1 ± 13.2	68.1 ± 9.9
Mean BMI (±SD) (kg/m^2)	25.9 ± 3.9	25.9 ± 3.1
Current diabetes treatment		
Diet alone	47	52
Diet + α-glucosidase inhibitor	0	0
Diet + biguanide	22	19
Diet + low dose of sulfonylurea	31	29
Mean HbA1c (±SD) (%)	8.8 ± 2.2	8.9 ± 1.9
Mean FPG (±SD) (mg/dl)	177.5 ± 63.5	185.9 ± 61.3

The figures in the table denote percentage unless specified otherwise as a mean value (±SD).
BMI, body mass index; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; SD, standard deviation.

samples. Subgroups with FAS1 and FAS2 of efficacy criteria were described according to previous treatment for diabetes at inclusion.

Results

The two treatment groups were comparable for all baseline characteristics (table 1). A total of 58 and 61 patients were included in the FAS1 and FAS2 efficacy analysis respectively. The mean baseline values of HbA1c on FAS1 (FAS defined for HbA1c) were 8.8 ± 2.2% in the gliclazide MR group and 8.8 ± 2.0% in the gliclazide group; the mean baseline FPG values on FAS2 (FAS defined for FPG) were 177.5 ± 63.5 mg/dl in the gliclazide MR group and 188.2 ± 62.6 mg/dl in the gliclazide group.

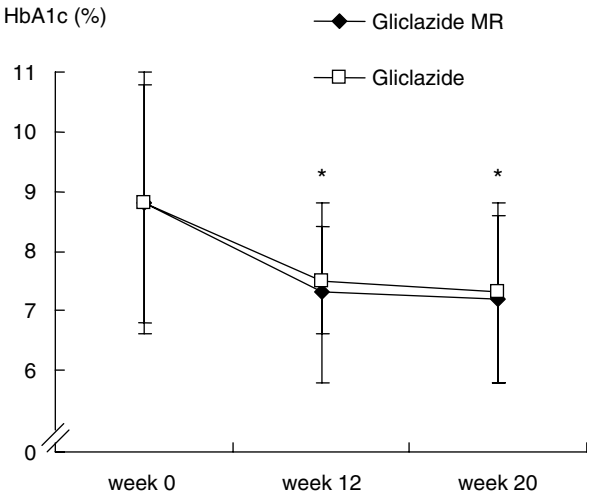

Fig. 2 Evolution of haemoglobin A1c (HbA1c) after treatment by gliclazide and gliclazide-modified release. Change in mean HbA1c (mean ± SD) over 20 weeks treatment period in patients with regard to anti-diabetic therapy. In both groups, a significant decrease in HbA1c from baseline was maintained over time (paired *t*-test within treatment group; *p < 0.001) but no difference between treatment groups (two-way ANOVA; p = 0.947).

In FAS1, within-group analysis demonstrated that gliclazide MR and gliclazide significantly decreased the values of HbA1c at week 20/last visit by 1.6 ± 1.6% (p < 0.001) and 1.6 ± 1.4% (p < 0.001), respectively, and there is no difference between treatment groups (p = 0.947) (figure 2).

Subgroup analysis showed that significant decrease in HbA1c regardless of treatment group was observed irrespective of pre-existing therapy for diabetes: −2.3 ± 1.5% (p < 0.001) for patients on diet alone, −0.6 ± 1.3% (p < 0.001) for patients switched from sulfonylurea to study drug and −1.4 ± 0.8% (p < 0.001) for patients on metformin in combination with study drug (figure 3).

In FAS2, gliclazide MR decreased FPG over the treatment period by −40.8 ± 56.3 mg/dl (p < 0.001) and gliclazide by −24.5 ± 67.0 (p = 0.059) (figure 4 and table 2). As for HbA1c, subgroup analysis showed the decrease of FPG in the two groups irrespective of pre-existing therapy for diabetes (table 3).

A total of 63 patients were evaluated for safety. Two patients who were given study medication were lost to follow-up at week 0. As a consequence, all description of frequency on safety set was made on 61 patients.

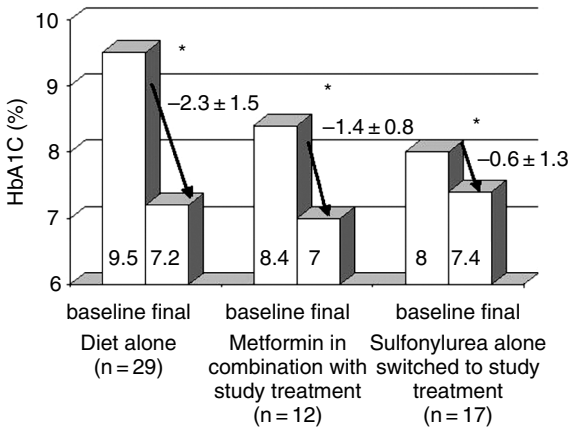

Fig. 3 Evolution of haemoglobin A1c (HbA1c) in subgroups within FAS1. Change in mean HbA1c (mean ± SD) over 20 weeks treatment period in patients with regard to anti-diabetic therapy. In both groups, a significant decrease in HbA1c from baseline was maintained over time (paired *t*-test within treatment group; *$p < 0.001$).

In the gliclazide MR group, the most common adverse effects were abdominal pain (9%) and pharyngitis (9%), while in the gliclazide group the most common adverse effect was neuropathy (14%). Regardless of treatment, most of the adverse effects were mild in severity. Among these adverse events, only two were drug-related, one for increase of aminotransferase level and the other for skin rash. Two serious adverse events, one each for cholangiocarcinoma and bladder cancer, were reported from two patients in the gliclazide group, but none was considered related to treatment.

Three patients (9.3%) experienced five mild hypoglycaemic episodes in the gliclazide MR treatment group. One of the patients reported non-compliance with the diet and excess physical activity and two did not report triggering factors. No suspected hypoglycaemic episode was observed in the gliclazide treatment group. No major episodes (external assistance required) were reported.

No clinically significant changes of vital signs (systolic blood pressure, diastolic blood pressure and heart rate) from baseline were observed in the two treatment groups during the study period (data not shown). At the end of the study treatment period, the mean changes of body weight were 1.4 ± 2.7 kg in the gliclazide MR group and 1.4 ± 2.7 kg in the gliclazide group. This evolution is likely related to the large improvement of blood glucose control in both treatment groups.

All biological parameters (haematology, biochemistry and lipids) were comparable at baseline in each treatment group. Some patients in either the gliclazide MR or the gliclazide groups had some haematology or biochemistry values outside the normal range at baseline and at final visit, but none of these laboratory values were clinically significant (data not shown). The changes from baseline to last value under treatment observed on all mean lipid parameters were small and with no clinical significance (table 4).

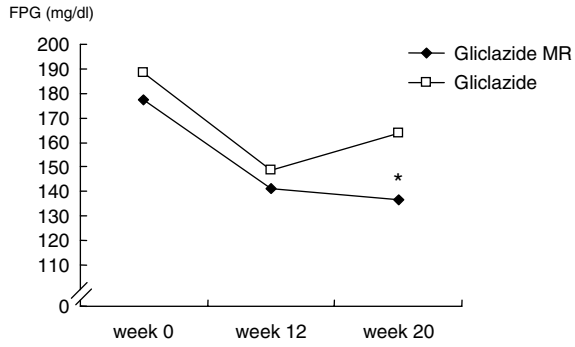

Fig. 4 Evolution of fasting plasma glucose (FPG) after treatment by gliclazide and gliclazide-modified release (gliclazide-MR) (FAS2). Change in mean FPG over 20 weeks treatment period in patients with regard to anti-diabetic therapy. In Gliclazide-modified release group, a significant decrease in mean FPG from baseline was maintained over time (paired *t*-test within treatment group; *$p < 0.001$) but not gliclazide group ($p = 0.059$).

Discussion

Type 2 diabetes is a metabolic disorder characterized by a combination of insulin secretion alteration and decreased insulin action resulting in chronic hyperglycaemia [5]. Gliclazide, as a potent oral hypoglycaemic agent for treatment of type 2 diabetes, acts mainly through the insulin secretory capacity [6]. Gliclazide MR is a new pharmaceutical formulation of gliclazide with modified-release characteristics, allowing a once-daily dosing regimen. Its release profile, with more than 50% of the active principle released within the first 4–6 h, can properly address diurnal hyperglycaemia and to avoid excessive release during the night, with the aim of keeping the good safety and efficacy profile of the standard formulation.

Table 2 Analysis of fasting plasma glucose for full analysis set 2 (FAS2) of the 61 patients randomized to receive gliclazide-modified release (gliclazide MR) or gliclazide

Value in visit (mg/dl)	Gliclazide MR	Gliclazide	Difference
W0 (baseline)	n = 32	n = 29	
Mean ± SD	177.5 ± 63.5	188.2 ± 62.6	−10.70
Median	157.5	163.0	
Range	(87.0–326.0)	(89.0–294.0)	
95% CI	154.6, 200.4	164.4, 212.0	−43.10, 21.62
p-Value*			0.471
Week 4	n = 32	n = 29	
Mean ± SD	163.3 ± 48.7	159.4 ± 53.3	3.90
Median	150.5	146.0	
Range	(95.0–323.0)	(81.0–305.0)	
95% CI	145.8, 180.9	139.1, 179.7	−22.21, 30.07
Week 8	n = 30	n = 27	
Mean ± SD	144.6 ± 25.6	149.8 ± 45.3	−5.20
Median	147.5	142.0	
Range	(82.0–195.0)	(76.0–252.0)	
95% CI	135.0, 154.1	131.9, 167.7	−25.18, 14.76
Week 12	n = 30	n = 26	
Mean ± SD	141.0 ± 25.1	148.5 ± 47.8	−7.50
Median	141.0	138.0	
Range	(78.0–183.0)	(79.0–254.0)	
95% CI	131.6, 150.4	129.2, 167.8	−28.69, 13.61
Week 20/last visit	n = 32	n = 29	
Mean ± SD	136.7 ± 42.2	163.7 ± 67.9	−27.00
Median	130.0	141.0	
Range	(53.0–323.0)	(78.0–376.0)	
95% CI	121.5, 151.9	137.9, 189.6	−56.51, 2.50
Change from week 0 to week 20/last visit	n = 32	n = 29	
Mean ± SD	−40.8 ± 56.3	−24.5 ± 67.0	−16.30
Median	−19.5	−26.0	
Range	(−191.0 to 32.0)	(−129.0 to 242.0)	
95% CI	−61.1, −20.4	−50.0, 1.0	−47.87, 15.34
p-Value†	<0.001	0.059	
p-Value*			0.384

CI, confidence interval; SD, standard deviation.
*Two-way parametric ANOVA between treatment groups.
†Paired *t*-test within treatment group.

In this study, we found that gliclazide MR improved blood glucose control (HbA1c) to the same extent in type 2 diabetic patients when compared with the patients treated with gliclazide as a monotherapy or in combination with metformin. Concerning the change of FPG (FAS 2), gliclazide MR group showed a significant decrease of FPG but not in gliclazide group over the 20-week treatment period. These results were comparable with the previously conducted international phase III [11].

With regard to the subgroups' analysis, the results showed that both treatments improved blood glucose control irrespective of pre-existing therapy for diabetes.

It is recognized that a once-daily regimen should improve long-term compliance in the treatment of chronic diseases, such as diabetes mellitus [12]. In this study, we found that overall compliance was excellent in both treatment groups. Because the study was designed as double blind with two administrations per day, we were not able to evaluate the beneficial effect of a once-daily administration.

The general safety of gliclazide MR and gliclazide was good with a similar incidence of adverse events. Regardless of treatment, most of the adverse events were mild in severity. Only two adverse events (one

Table 3 Analysis of change of fasting plasma glucose from week 0 to last value for subgroup within full analysis set 2 (FAS2)

Subgroup	Gliclazide MR	Gliclazide
Diet alone		
Patient number	15	15
Net FPG change*	−63.2 ± 62.1	−37.7 ± 52.5
Sulfonylurea alone switched to study treatment		
Patient number	10	9
Net FPG change*	−10.3 ± 36.2	−5.4 ± 97.1
Metformin in combination with study treatment		
Patient number	7	5
Net FPG change*	−36.1 ± 51.0	−19.2 ± 37.5

*Data for net fasting plasma glucose (FPG) change are mean ± SD.

for increase of aminotransferase level in the gliclazide MR group and one for skin rash in the gliclazide group) were considered as related to the study treatment.

In the literature, episodes of hypoglycaemia have been reported during treatment, with an incidence ranging from 3.8% to 16.7% in the patients receiving gliclazide and 5.2% in those receiving gliclazide MR [11,13]. In this study, three patients (9.3%) experienced five mild hypoglycaemic episodes in the gliclazide MR group and none in the gliclazide group. One of the patients reported non-compliance with the diet and excess physical activity. No major hypoglycaemic episode (external assistance required) was reported. Because of small case number of patients who reported hypoglycaemia, we were not able to draw any conclusion on incidence of hypoglycaemic episodes.

All vital sign parameters were comparable at baseline. No clinically significant changes of vital signs (systolic blood pressure, diastolic blood pressure and heart rate) from baseline were observed in the two treatment groups during the study period. The mean changes of body weight were 1.4 ± 2.7 kg in the gliclazide MR group and 1.4 ± 2.7 kg in the gliclazide group. This weight gain in both groups is likely related to the significant improvement of blood glucose control [14].

Although some patients in either the gliclazide MR or the gliclazide groups had some haematology or biochemistry values outside the normal range at baseline and at final visit, none of these laboratory values were clinically significant. The changes from baseline to last value under treatment observed on all mean values of lipid parameters were small and with no clinical significance except fasting LDL-C. The fasting LDL-C level, however, was observed to reach a clinically and statistically significant ($p = 0.029$) decrease after 20-week treatment in the glicazide MR group.

Conclusions

Our study suggested that gliclazide MR and gliclazide decreased HbA1c to the same extent in type 2 diabetic patients treated with gliclazide as a monotherapy or in combination with metformin. In the decrease of FPG, gliclazide MR showed significant decrease in FPG but not in gliclazide group probably due to the better compliance of gliclazide MR [15]. Both drugs were very well tolerated with a very small number of patients having reported hypoglycaemic episodes.

Table 4 Analysis of changes of lipids from W0 to W20 and last visit

	Gliclazide MR			Gliclazide		
Variable (mg/dl)	(week 0)	(week 20)	p-value†	(week 0)	(week 20)	p-value†
Fasting TG	n = 31	n = 31		n = 26	n = 26	
	146.2 ± 92.5	150.4 ± 66.7	0.690	183.2 ± 191.3	215.1 ± 237.4	0.177
Fasting TC	n = 31	n = 31		n = 26	n = 26	
	206.9 ± 28.1	196.4 ± 33.9	0.078	205.0 ± 38.0	208.2 ± 40.5	0.627
Fasting HDL-C	n = 29	n = 29		n = 25	n = 25	
	43.8 ± 8.0	43.8 ± 8.4	0.971	49.4 ± 13.4	48.1 ± 13.4	0.351
Fasting LDL-C	n = 30	n = 30		n = 24	n = 24	
	136.1 ± 32.3	120.8 ± 34.8	0.029*	132.1 ± 28.9	127.5 ± 35.6	0.497

*$p < 0.05$; †Paired *t*-test within treatment group.

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