J Med Sci 2010;30(1):021-027
http://jms.ndmctsgh.edu.tw/3001021.pdf

A Randomized, Open-Labeled and Controlled Study of the Efficacy and Safety of Kludone Modified Release in the Treatment of Chinese Type 2 Diabetic Patients

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Background: The aim of this study was to evaluate the efficacy and safety profile of Kludone modified release (MR) in Chinese patients with type 2 diabetes. **Methods:** Thirty-three Chinese patients with type 2 diabetes on diet control and low-dose sulfonylurea were randomized to Kludone MR or Diamicron MR once daily. Drug doses were increased at 4 week intervals from 30 mg to 120 mg until metabolic control was achieved or the maximum dose reached. Efficacy was evaluated by the fasting plasma glucose and hemoglobin A1c (HbA1c) levels. **Results:** Fasting plasma glucose significantly decreased from 178.4±38.7 mg/dL to 157.1±39.4 mg/dL (p<0.01) in the Diamicron MR group, but was not significant in the Kludone MR group after 4 weeks (p=0.084). After 12 weeks of treatment, fasting plasma glucose decreased from 178.4±38.7 mg/dL to 156.0±42.1 mg/dL (p<0.01) in the Diamicron MR group and from 156.2± 45.1 mg/dL to 145.3±45.6 mg/dL (p=0.163) in the Kludone MR group. Hemoglobin A1c between groups was not statistically different (p=0.687), indicating the efficacy of treatment was similar. No adverse event led to withdrawal of the medication. No major episodes were reported in either treatment groups. **Conclusion:** Once-daily Diamicron MR showed a better trend in improving fasting plasma glucose control compared to Kludone MR regardless of the initial diabetes treatment. However, neither Kludone MR nor Diamicron MR significantly decreased HbA1c levels in this study with limited case numbers. Both drugs were well tolerated with a very small number of patients reporting hypoglycemic episodes.

Key words: kludone-modified release, type 2 diabetic mellitus, diamicron-modified release, sulfonylurea, gliclazide-modified release

INTRODUCTION

The major therapeutic goal in patients with type 2 diabetes, besides the control of blood pressure and lipid levels, is to optimize glycemic control to reduce the development and/or the severity of long-term diabetic complications. Sulphonylureas are widely used in managing type 2 diabetes as impaired insulin secretion plays an important role in the pathophysiology of hyperglycemia.[1] Tight glycemic control is essential to prevent or delay diabetes complications.[2,3] One drawback of tightening glycemic control is the risk of hypoglycemia.[3] Moderate hypoglycemia induces cognitive impairment,[4] and many complex attention tasks relevant to everyday life may be impaired.[5] Recurrent severe hypoglycemia may induce impaired awareness of hypoglycemia and possibly long-term sequelae in the form of cumulative cognitive impairment.[6,7]

In the UK Prospective Diabetes Study (UKPDS 35), a 1% difference in mean hemoglobin A1c (HbA1c) was associated with a significant decrease in deaths (21%). Further, this 1% difference resulted in 37% less microvascular complications, and a 14% to 43% decrease in macrovascular complications related to diabetes.[8] Although exercise and diet remain the cornerstones of therapy, pharmacological treatment is usually required. One such pharmacological treatment is using sulfonyl-

Received: September 2, 2009; Revised: November 13, 2009; Accepted: December 8, 2009
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urea-based drugs, including Gliclazide-modified release (Gliclazide MR or Diamicron MR).[9,10] Gliclazide is the major active component of both Gliclazide MR and Diamicron MR. Gliclazide-modified release (Gliclazide MR or Diamicron MR) is a new once-daily sulfonylurea proposed to be of benefit in polymedicated diabetic patients, whose compliance rate has been shown to be poor, as in most chronic diseases.[11,12] Thus, a once-daily intake of Diamicron MR at breakfast progressively increases plasma concentrations to yield a relative plateau between 3 h and 12 h with a time to peak concentration around 6 h and a subsequent decrease over the following 12 h.[13] Consistent with this pharmacokinetic profile, Diamicron MR has been shown to be effective over 24 h.[14]

Gliclazide MR has shown to be effective and safe,[15-17] but a smaller incidence of hypoglycemia has been reported with Gliclazide than with other sulphonylureas in several studies.[18-20] Kludone MR is a sulphonylurea composed of a Gliclazide MR once-daily dosage, manufactured and approved in Taiwan. This study was a bioequivalence study, aimed to evaluate the efficacy and safety profile of a Kludone MR compared with Diamicron MR in Chinese patients with type 2 diabetes.

METHODS

Study population

This was an open-labeled, randomized study conducted in Chinese patients with type 2 diabetes (Figure 1). Patients were eligible to enter the run-in period of the study if they fulfilled the following criteria: male or female outpatients aged from 21 to 75 years with a body mass index ranging from 23 to 35 kg/m^2 with type 2 diabetes known for at least 3 months. Diabetes was treated with diet for ≥ 3 months, 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. Patients had HbA1c values ≥ 7.0% and ≤ 11.0% obtained within 3 month before study entry. Fasting plasma glucose levels measured from 120 to 250 mg/dL after a 1-week period of wash-out period of previous oral antidiabetic drug. Patients had to have the ability to comply with the study protocol and cooperate during the study. The study was approved by the Tri-Service General Hospital Ethics Committee. After explaining the study procedures and protocol to the participants at the time of physical examination, informed written consents were obtained from the subjects before the study began. Efficient contraception was used by female patients with child-bearing potential.

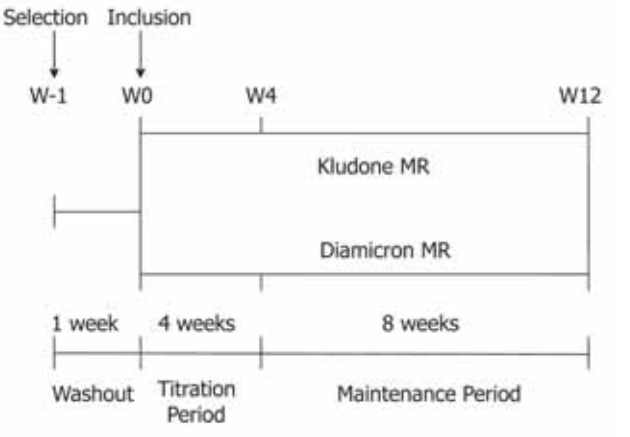

Fig. 1 An open-labeled, randomized study was conducted in Chinese patients with type 2 diabetes.

Exclusion criteria included 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 insulin action-like lipoatrophic diabetes, hemochromatosis, endocrinopathies, poorly controlled diabetes (due to intercurrent illness, infection, or surgery), ketoacidosis, history of allergy to sulfonamides, concomitant treatments affecting glucose metabolism or Gliclazide metabolism, endocrine diseases other than diabetes, immunosuppression, surgical procedures (either recent or planned during the study), pregnancy or lactation, drug or alcohol abuse, participation in another study in the previous 3 months, serum creatinine >1.5 mg/dL, aminotransferase or alkaline phosphatase greater than threefold upper normal range, and uncooperative or unreliable patients. Also, conditions related to concomitant diseases, such as acute and chronic conditions other than diabetes that could preclude end-point evaluation or progress in the study (e.g., all factors or diseases interfering with HbA1c analysis, including serious anemia, hemoglobinopathy, hemolysis, and blood clotting) resulted in exclusion from the study.

Study design and drug regimen

The patients entered a 1-week wash-out period after selection. Patients were asked to continue their usual treatment without changing the dose in combination with the study drug, and dietary advice was reinforced. At the initial visit (week 0), the patients were randomized on either Kludone MR 30 mg (bioequivalent product of Gliclazide-modified release, Pharmosa Limited Co., Tai-Chung, Taiwan) or Diamicron MR 30 mg (originally

developed formulation of Gliclazide-modified release, Sevier Lab Inc., Neuilly-sur-Seine, France) for 12 weeks.

From the week-0 visit to the week-4 visit, patients entered a 4-week therapeutic adjustment period (titration period). Patients started with the lowest dose (Kludone MR 30 mg or Diamicron MR 30 mg), and the dosage was gradually increased at each 1-week visit to achieve optimal glycemic control (fasting plasma glucose ≤ 120 mg/dL) or maximum dose (120 mg/day). At the end of the titration period (week-4 visit), patients commenced an 8-week maintenance period. During this time the dosage remained unchanged. Regardless of treatment and dosage, the patients took one to four tablets each morning before breakfast. Tablets were ingested with 100 mL of drinking water.

Efficacy and Safety Assessment

Efficacy was measured by HbA1c, which was assessed in the laboratory of Tri-Service General Hospital at week-0, week-4, and week-12 visits. Fasting plasma glucose was assessed in the laboratory of Tri-Service General Hospital at week-0, week-1, week-2, week-3, week-4, week-8, and week-12 visits. Weight, body mass index, blood pressure, and heart rate were recorded at week-0 and week-12 visits. Hematology, biochemistry (sodium, potassium, creatinine, alkaline phosphatase, aminotransferase, and total proteins), and lipids (triglyceride, TG; total cholesterol, TC; low-density lipoprotein cholesterol, LDL-C; and high density lipoprotein-cholesterol, HDL-C) were also assessed in the laboratory of Tri-Service General Hospital at week-0 and week-12 visits.

Safety and tolerance were chiefly assessed from adverse events spontaneously reported and described by the patients at each visit with special attention to the severity of hypoglycemia. This was evaluated by the occurrence of symptoms suggestive of hypoglycemia recorded in the patient's diary. Severity of symptoms suggestive of hypoglycemia was rated in four grades: grade 1 (mild and transient symptoms), grade 2 (transient inability to pursue usual activities), grade 3 (need for external assistance), and grade 4 (need for medical assistance). Safety as it relates to hypoglycemia was expressed as at least one episode of symptoms suggestive of hypoglycemia during the study period. For assessing other adverse events, patients were asked to record the types of adverse events in their diary during the study period. Serious adverse events were defined as events resulting in death, persistent or significant disability or incapacity, hospitalization or prolongation of preexisting hospitalization, severe hypoglycemia, and life-threatening events. Acute intoxication, important medical events, and pregnancy were considered serious events. In addition, routine blood and biochemistry tests were performed before randomization (week 0) and at the end of the trial (week 12). At each visit, unused tablets and empty blister packs were returned and counted to assess patient compliance with the study protocol.

Table 1 Baseline characteristics of study patients randomized to Kludone-modified release or Diamicron-modified release

Baseline characteristics	Kludone MR (n=14)	Diamicron MR (n=14)	*p*-value
Age	60.6±9.0	58.2±12.3	NS
Male (n[%])	7 [50.0]	8 [57.1]	NS
Height (cm)	159.8±5.8	163.5±6.8	NS
Weight (kg)	63.7±9.2	67.2±10.9	NS
BMI (kg/m^2)	25.03±4.05	25.16±4.07	NS
SBP (mmHg)	126.3±11.9	127.5±10.5	NS
DBP (mmHg)	76.9±10.7	74.7±11.0	NS
MBP (mmHg)	109.8±10.8	109.9±8.5	NS
HR (/min)	70.8±8.1	74.9±7.3	NS
AST (U/L)	23.0±7.9	26.7±11.8	NS
ALT (U/L)	21.6±10.6	30.8±17.2	NS
Cr (mg/dL)	0.81±0.26	0.87±0.22	NS
FPG (mg/dL)	156.2±45.1	178.4±38.7	NS
HbA1c (%)	8.04±0.76	8.26±1.11	NS

Data represents percentage unless specified as mean value (±SD). MR, modified release; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Cr, creatinine; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; SD, standard deviation; NS, not significant.

Statistical Analysis

The main analysis was the analysis of the mean changes at each visit from baselines values in each treatment group using a paired Student *t* test. Comparisons of fasting plasma glucose and HbA1c between the two treatment groups were made at different time points during the trial period using two-way analysis of variance, and $p<0.05$ was considered statistically significant. Data were expressed as mean±SD. For the evaluation of safety, changes in biological parameters over time were described for each treatment group. Baseline and end of study values (week-0 and week 12, respectively) were compared in both treatment groups using paired *t*-test. All statistical analyses were performed using SPSS 14.0 for Windows.

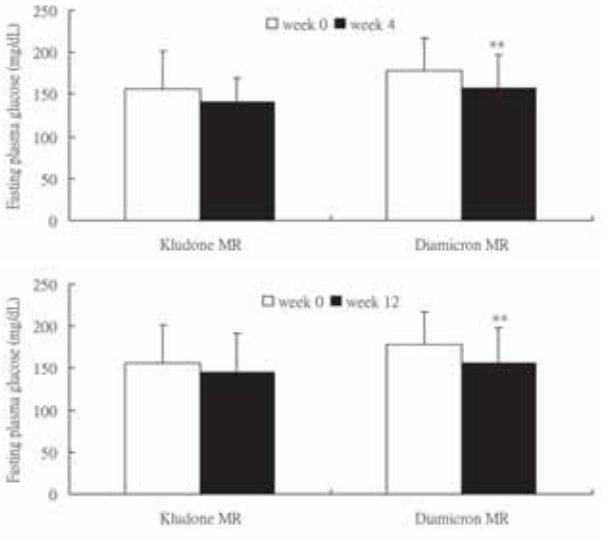

Fig. 2 Evolution of fasting plasma glucose after treatment by Kludone-modified release and Diamicron-modified release is shown. Change in fasting plasma glucose was noted over 4 (A) and 12 (B) weeks of treatment with anti-diabetic therapy. Within-group analysis demonstrated that Diamicron-modified release significantly decreased fasting plasma glucose at weeks 4 and week 12.

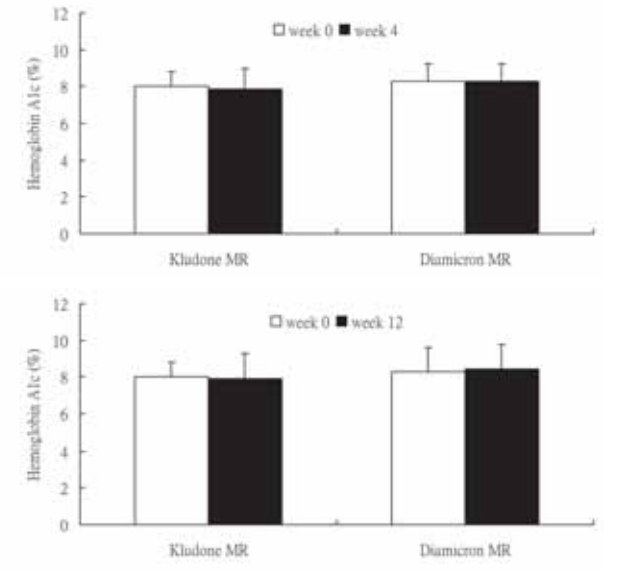

Fig. 3 Evolution of hemoglobin A1c after treatment by Kludone-modified release and Diamicron-modified release is shown. Change in mean hemoglobin A1c (mean+SD) over 4 and 12 weeks is shown. Within-group analysis demonstrated that Kludone-modified release and Diamicron-modified release have no statistically difference in hemoglobin A1c at weeks 4 (A) and 12 (B).

RESULTS

The two treatment groups were comparable for all baseline characteristics (Table 1). Fourteen patients from each treatment group (Kludone MR, Diamicron MR) were included in the fasting plasma glucose and HbA1c efficacy analysis. The mean baseline fasting plasma glucose values were 156.2±45.1 mg/dL in the Kludone MR group and 178.4±38.7 mg/dL in the Diamicron MR group (Table 1). The mean baseline values of HbA1c were 8.04±0.76% in the Kludone MR group and 8.26 ±1.11% in the Diamicron MR group (Table 1). Within-group analysis demonstrated the Diamicron MR group had significantly decreased the values of fasting plasma glucose at the week-4 visit (-21.2±24.5 mg/dL) ($p<0.01$, Figure 2A) and at the week-12 visit (-22.3±26.0 mg/dL) ($p<0.01$) (Figure 2B). However, Kludone MR group experienced no significant decreases in fasting plasma glucose at the week-4 visit (-16.0±32.1 mg/dL) (p=0.084, Figure 2A) and at the week-12 visit (-10.9±27.7 mg/dL) (p=0.163, Figure 2B).

Within-group analysis demonstrated both the Kludone MR and Diamicron MR groups did not decrease values of HbA1c at the week-4 visit (0.18±0.75%) (p=0.391) and -0.03±0.74% (p=0.887), respectively (Figure 3A). Within-group analysis demonstrated both groups had not significantly decreased values of HbA1c at the week-12 visit by 0.11±1.32% in the Kludone MR group (p=0.752) and -0.20±1.05% in the Diamicron MR group (p=0.489) (Figure 3B). No statistically significant difference was found in HbA1c levels between the Kludone MR and the Diamicron MR groups (p=0.687) after 12 weeks of treatment, indicating the efficacy of treatment was similar.

Five patients who were given study medication were lost to follow up at week 0. Consequently, descriptions of frequency on the parameter of safety were made on 28 patients. In the Diamicron MR group, 1 patient experienced 2 mild hypoglycemic episodes, and 1 patient experienced chest discomfort and heartburn sensation. The main reason for the mild hypoglycemic episodes was related to good plasma glucose control. One of the patients reported an increased regular heart rate and 1 patient experienced muscle pain over both lower limbs in the Kludone MR group. No suspected hypoglycemic episode was noted in the Kludone MR group. No adverse event led to withdrawal of the medication. No major episodes requiring external assistance were reported in the

Table 2 Analysis of lipids from week 0 to week 12 in study patients randomized to Kludone-modified release or Diamicron-modified release

	Kludone MR			Diamicron MR		
Variable (mg/dL)	Week 0	Week 12	*p*-value	Week 0	Week 12	*p*-value
Fasting TG	109.5±44.8	91.5±35.4	0.292	139.2±101.7	104.6±37.4	0.298
Fasting TC	165.0±30.3	130.6±24.9	0.060	177.0±37.2	176.5±28.4	0.951
Fasting LDL-C	114.8±21.5	90.6±24.6	0.052	125.0±21.9	110.6±34.2	0.459
Fasting HDL-C	53.7±14.6	55.3±9.3	0.755	51±9.4	50±6.0	0.562

Paired t-test was used to compare the difference within treatment group. MR, modified release; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

two treatment groups. No clinically significant changes in vital signs or any biological parameter (hematology or biochemistry), including lipid levels, from the baseline were observed in the treatment groups during the study period.

DISCUSSION

Pharmacological treatment of hyperglycemia should address both the abnormalities of type 2 diabetes mellitus, that is reduction of insulin resistance and restoration of normal insulin secretion.[21] Gliclazide, as a potent oral anti-diabetic drug for the treatment of type 2 diabetes, mainly acts through the insulin secretory capacity.[22] Gliclazide MR is a new pharmaceutical formulation of Gliclazide with modified-release characteristics, allowing a once-daily dosing regimen. The hydrophilic matrix of the hypromellose-based polymer in the new formulation leads to a progressive release of the drug, matching the 24 h glycemic profile in untreated patients with type 2 diabetes mellitus.[23] Its release profile can properly address diurnal hyperglycemia and prevent excessive release during the night. The new formulation maintains the good safety and efficacy profile of the standard formulation.[15-17] The aim of this study was to evaluate the efficacy and safety profile of Kludone MR in Chinese patients with type 2 diabetes.

In this study, we found Kludone MR had same blood glucose control (HbA1c) in Chinese patients with type 2 diabetes compared with patients treated with Diamicron MR. Fasting plasma glucose significantly decreased in the Diamicron MR group, but not in the Kludone MR group after 4 weeks of treatment. It is recognized a once-daily regimen should improve long-term compliance in treating chronic diseases such as diabetes mellitus.[24] In this study, we found overall compliance was excellent in both treatment groups.

The general safety of Kludone MR and Diamicron MR was good with a similar incidence of adverse events. Arthritis, back pain, dizziness, somnolence, headache, diarrhea, nausea, and confusion are possible side effects associated with the use of Gliclazide MR tablets.[25] Regardless of treatment, most adverse events were mild in severity. Only 2 adverse events (1 patient who experienced 2 mild hypoglycemic episodes in the Diamicron MR group, and 1 patient who experienced increased heart rate in the Kludone MR group) were considered to be related to the study treatment. No adverse event led to the withdrawal of the medication. No major episodes were reported in the two treatment groups. Because of the small number of cases with reported mild hypoglycemia, we were not able to draw any conclusion on the incidence of hypoglycemic episodes.

All vital sign parameters were comparable at baseline and final visit. No clinically significant changes in vital signs (weight, body mass index, systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate) from the baseline were observed in the two treatment groups during the study period (data not shown). The biological parameters (including hematology and biochemistry) were comparable at baseline and at the final visit in each treatment group. Although some patients in either the Kludone MR treatment or the Diamicron MR groups had some hematology or biochemistry values outside the normal range at the baseline and the final visit, none of these laboratory values were clinically significant (data not shown). There was also no noticeable change in electrocardiogram at the baseline and the final visit.

All lipid profiles were comparable at the baseline and the final visit. The mean baseline fasting TG levels were 109.5±44.8 mg/dL in the Kludone MR group and 139.2 ±101.7 mg/dL in the Diamicron MR group. The mean baseline values of fasting TC were 165.0±30.3 mg/dL in the Kludone MR group and 177.0±37.2 mg/dL in the Diamicron MR group. The mean baseline values of fasting LDL-C were 114.8±21.5 mg/dL in the Kludone MR group and 125.0±21.9 mg/dL in the Diamicron MR group (Table 2). Within-group analysis demonstrated the Kludone MR group (p=0.292) and the Diamicron MR group (p=0.298) had no significantly decreased fasting TG values at the week-12 visit (Table 2). The changes from the baseline to the last value at final visit on all mean lipid parameters were small and not clinically

significant (Table 2). However, the Kludone MR group seems to have same effects on the decreasing values of fasting TC (p=0.060) and LDL-C (p=0.052) at week-12 visit.

Our study suggested there was no significant difference in the blood glucose control (HbA1C) between the Kludone MR group and Diamicron MR group in Chinese patients with type 2 diabetes. The Diamicron MR group showed significant decreases in fasting plasma glucose that were not observed in the Kludone MR group. This may have been due to the limited case number. Both drugs were very well tolerated with a very small number of patients reporting hypoglycemic episodes.

ACKNOWLEDGMENTS

The authors appreciate Dr. Kai-Shun Chen, Dr. Chu-Dang Tsai, Dr. Chen-Hao Tsai and Dr. Szu-Han Chiu for reviewing the manuscript, and Miss Feng-Ying Mo and Yen-Chin Chiu for their excellent secretarial assistance. This study was supported by Tri-Service General Hospital (TSGH-C96-5-S03), Taipei, Taiwan, R.O.C. and pharmaceutical factory of United Biomedical Inc. Asia/Pharmosa, Tai-Chung, Taiwan, R.O.C. The personnel, manuscript writing and statistical analysis were fully provided by Tri-Service General Hospital and School of Public Health, National Defense Medical Center, Taipei, Taiwan, R.O.C.

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