Endocrine, *vol. 13, no. 1, 117–121, August 2000* 0969–711X/00/13:117–121/$11.25

Appropriate Timing of Glimepiride Administration in Patients with Type 2 Diabetes Millitus

A Study in Mediterranean Countries

Ramon Gomis,[1] Sotirios A. Raptis,[2] and Ramon Ravella[3]

Endocrinology and Diabetes Unit., IDIBAPS, Hospital Clínic, School of Medicine, Barcelona University, Barcelona, Spain.
Second Dept. of Internal Medicine "Propedeuntic Athens University," Evangelismos Hospital, Athens, Greece.
Research and Development Department, Hoechst Marion Roussel, S. A. (Spain), Barcelona, Spain.

Sulfonylureas are used to treat patients with type 2 diabetes mellitus when diet and exercise fail. Glimepiride, a new sulfonylurea, can be administered in one daily dose, thanks to its pharmacokinetic properties. We attempted to establish the optimal time of day for the administration of Glimepiride in a group of patients from the Mediterranean area by clinical trial. No relationship was found between the time of administration and fasting blood glucose values, or HbA_{1c}, or the frequency or severity of hypoglycemic episodes.

Key Words: Diabetes mellitus; sulfonylureas; Glimepiride; diet.

Introduction

Increasing evidence from epidemiological studies suggests that poor metabolic control, hyperglycemia, and dislypemia, are associated with an increased risk of micro- and macrovascular complications in patients with type 2 diabetes mellitus (NIDDM) *(1)*. The initial nonpharmacological treatment is to introduce changes in lifestyle, nutrition, and exercise. However, in the course of diabetes, β-cell function decreases, and after many years of clinical evolution, diet and exercise are insufficient to facilitate optimal metabolic control *(2)*.

When these measures are unsuccessful, pharmacotherapy is required *(3,4)*. Sulfonylureas (SU) have been used since the 1950s as a first-line therapy for type 2 diabetes mellitus patients. However, there are still some aspects of conventional hypoglycemic medication that could be better adjusted for the patients, which justifies the development of a new antidiabetic SU. For instance, emphasis has been placed on potency, but little attention has been paid to the dynamics of insulin secretion *(5)*.

Glimepiride is an oral SU, developed as a result of the search for agents with potential therapeutic advantages over second-generation drugs *(6)*. Its effect on glycemia is based on the stimulation of insulin secretion from the β-pancreatic cells, acting on a specific receptor (SUR) and closing the ATP potassium channels. Previous clinical trials showed that once-daily administration provides acceptable metabolic control for 24 h: a daily dose from 1 to 8 mg of Glimepiride is equivalent to 2.5–20 mg of Glibenclamide. Moreover, it facilitates patients compliance *(7,8)*. Taking into account the interaction between the dynamics of insulin secretion stimulated by Glimepiride and the dynamics of glycemia after meals, nutritional behavior should be noted. However, the optimum moment for the intake of SU, including Glimepiride, has not been examined in controlled clinical trials in Mediterranean countries. Because the size of the meals and the distribution of nutrients per meal in the Mediterranean area differ from other European countries, it is important to establish the optimum meal at which to take Glimepiride *(9)*.

The aim of this study was to investigate the best time of the day for the administration of Glimepiride in type 2 diabetic patients, in the Mediterranean area.

Patients and Methods

Study Design

The trial was multicentered (17 sites in the Mediterranean area), prospective, double-blind, placebo-controlled, parallel, and randomized. The study consisted of a 2–12 wk titration phase, followed by a 24-wk maintenance phase in patients with type 2 diabetes mellitus.

The clinical study protocol and the informed consent documents were reviewed and approved by an independent ethics committee at each study site. Informed consent was obtained and all requirements were consistent with the ethical principles of the Declaration of Helsinki.

Received March 22, 2000; Revised May 24, 2000; Accepted May 24, 2000.
Author to whom all correspondence and reprint requests should be addressed: Dr. Ramon Gomis, Endocrinology and Diabetes Unit, Villarroel, 170 Barcelona 08036, Spain. E-mail: gomis@clinic.ub.es

All patients were treated by active drugs plus placebo according to the following protocol.

After dose adjustments (increasing doses between 1 and 6 mg, once a day, before the main meal) to achieve acceptable metabolic control, the patients were assigned to receive: A) Glimepiride before breakfast and placebo before lunch and dinner, B) Glimepiride before lunch and placebo before breakfast and dinner, and C) Glimepiride before dinner and placebo before breakfast and lunch. The daily dose achieved in the titration phase was maintained during the maintenance phase. However, the dose could be changed if required to avoid severe hypoglycemic episodes.

Selection of Subjects

Eligible patients were 40–70 yr of age, with a body mass index (BMI) of 20–30 kg/m^2 and with stable weight during the last 3 mo. In addition, they were also required to satisfy the following criteria: fasting blood glucose (FBG) between 70 and 180 mg/dL (3.9–10.0 mmL/L) and treatment for at least 3 mo, with glibenclamide (5–15 mg) or another SU at an equivalent dosage. The FBG was measured with a reflectometer (Accutrend ®mini, Boehringer Mannheim) in the first study visit (visit 1) and in the last two visits of the titration phase. All patients were instructed to follow a normocaloric diet according to the recommendations of the European Diabetes Policy Group.

Exclusion criteria were: antidiabetic treatment other than SU or a combination of SU with other antidiabetic drugs, clinical history of renal or hepatic disease, concurrent therapy with drugs that may interfere with the hypoglycemic action of SU, hypersensitivity to SU, use of *an investigational* drug within 4 wk before entering the study, and women of childbearing potential who were not using a safe contraceptive method.

A total of 264 patients with type 2 diabetes millites were enrolled in 17 study centers in Greece, Italy, and Spain.

Two hypothesis were the basis to calculate the sample size:

- The rate of answer to the study medication [number of patients with FBG 70 and 180 mg/dL (3.9–10.0 mmol/L)], and
- Glycated (or glycosylated) hemoglobin (HbA_{1c}) values at the end of the maintenance phase.

A difference ≥ 25% between the best and the worst therapeutic regimen and ≥ 1% for the variation of HbA_{1c} values (basal and final) were considered clinically relevant. A 22% dropout rate of patients (therapeutic failure, non-responder) was expected. In these conditions, considering a bilateral test with $\beta = 0.20$ and $\alpha = 0.05$, the minimum number of patients should be 240.

Data Collection

All the laboratory measurements were performed at a central laboratory (Dr. Odle Smithkline Beecham Clinical Laboratory, Belgium). The insulin and C-peptide were measured by RIA, the HbA_{1c} by chromatography, and the biochemistry by enzymatic methods. However, the measurements of pre- and postprandial glucose levels—on the days before visits 1,2,3,6, and 9—were performed by the patient, at home, using a reflectometer. The patients registered the results in their own diary.

Statistical Methods

The identification of the patients who were valuable for the analysis was carried out before opening the blind. Nonparametric tests were carried out if a parametric test could not be applied. All the tests were bilateral. Serum levels of HbA_{1c}, glucose, insulin, and C-peptide during the selection visit were analyzed by ANOVA. Response rate to the treatment was measured in the three groups by the Mantel–Haenszel test, taking into account the center effects. An analysis of covariance was used to measure the changes between basal and final values of HbA_{1c}, glucose, insulin, and C-peptide. For example, the final HbA_{1c} value was considered as the dependent variable, the basal value as the covariate, and the group and center as independent factors. Additional compositions of homogeneity were performed using the Kruskal–Wallis test.

Results

A total of 264 patients were divided at random into three groups, and given Glimepiride before breakfast (89), before lunch (85), and before dinner (90). The proportions were the same in each country. There were 166 men (63%) and 98 women (37%) included.

Basal Conditions

At entry, to measure the homogeneity of the treatment groups, the values of HbA_{1c}, insulin, C-peptide, glucose, and lipids during the selection visit were considered. The mean of HbA_{1c} ($p = 0.843$), insulin ($p = 0.883$), and C-peptide ($p = 0.704$) was similar in all three groups (breakfast, lunch, and dinner) at visit one, but there was a treatment effect on blood glucose levels ($p < 0.015$). These differences were tested with an ANOVA analysis.

As reported in Table 1, additional comparisons of homogeneity were performed for BMI, body weight, systolic and diastolic blood pressure, and no significant differences were found.

No differences were detected in the percentage of carbohydrates, fat or protein distribution, or in the total energy (kcal) (Table 2)

Efficacy

The response rate to the treatment was as follows: 73% of responders at breakfast, 75% at lunch, and 86% at dinner; nevertheless, by means of the Mantel–Haenszel test (stratifying the country effect), there was no significant difference between the three groups in the response rate ($p = 0.091$) (Table 3). The results reflect that the mean

Table 1
Comparison of Treatment Groups After Randomization (Visit 1) for Clinical Variables by Kruskal–Wallis Test

	Breakfast			Lunch			Dinner				
Variable	*n*	Median	Range	*n*	Median	Range	*n*	Median	Range	Test	*p* value
Body mass index [kg/m^2]	89	26.670	20.05–30.86	85	26.990	19.98–33.06	90	26.435	20.31–36.35	0.2793	0.8697
Body weight (kg)	89	73.0	43.5–100.0	85	72.0	46.5–95.3	90	71.9	45.7–105.0	0.3375	0.8447
Systolic blood pressure [mmHg]	89	140	110–180	85	140	100–180	90	130	100–182	1.9643	0.3745
Diastolic blood pressure [mmHg]	89	80	60–120	85	80	60–100	90	80	60–104	2.7697	0.2504

Table 2
Descriptive Statistics for Components of Daily Diet Recorded on Admission (Visit 1) and at Endpoint (Visit ≤9)

	Number	Admission		Endpoint		Change	
Variable	of patients	Mean	SD	Mean	SD	Mean	SD
Total carbohydrates (g)							
Breakfast	64	170.0	48.8	165.1	47.5	–4.9	38.8
Lunch	64	157.6	49.5	165.9	56.9	8.3	47.2
Dinner	67	158.4	51.3	151.4	47.3	–6.9	37.2
Total fat (g)							
Breakfast	64	59.7	24.4	61.4	26.8	1.8	16.7
Lunch	64	59.0	24.9	59.9	32.7	0.9	26.1
Dinner	67	56.1	22.6	56.7	21.2	0.6	9.4
Total protein (g)							
Breakfast	64	83.2	19.9	82.6	22.2	–0.1	12.2
Lunch	64	78.2	23.3	80.0	24.1	1.9	15.8
Dinner	67	78.6	21.9	78.1	19.0	–0.5	17.6
Total energy (kcal)							
Breakfast	64	1699	394	1679	445	–20	298
Lunch	64	1610	453	1632	512	22	422
Dinner	67	1585	397	1575	347	–10.5	206

change in HbA_{1c} is not especially significant among treatments taking into account the country of origin.

The decrease in HbA_{1c} from admission (visit 1) to endpoint (visit 9) and from visit 3 (after titration) to endpoint was evaluated by ANCOVA analysis, and there was no significant difference between treatments (Table 4). From visit 1 to endpoint, there was a decrease of 0.11% at breakfast, 0.11% at lunch, and 0.18% at dinner.

The same results were found for insulin, C-peptide, and blood glucose (Table 5).

Safety

Hypoglycemia is a secondary effect of sulfonylurea treatment; 9.3% of patients in the breakfast group presented at least one hypoglycemic episode during the maintenance phase, 16.3% in the lunch group, and 11.7% in the dinner group. These differences were not significant (chi-square test, $p = 0.409$). Moreover, the median of the number of hypoglycemic episodes per patient and the percentage of patients with hypoglycemia <60 mg/dL, showed similar results: no differences between treatments.

Total cholesterol, HDL-cholesterol, and triglycerides were compared. There was no treatment effect in any of these parameters, between endpoint values or after titration values. No adverse event related to the medication was detected.

Discussion

Dietary measures are considered a cornerstone in the treatment of type 2 diabetes mellitus together with programmed exercise to achieve an optimum metabolic control *(2)*. For a large number of patients this strategy is not sufficient. The next step in antidiabetic therapy is to use oral hypoglycemic agents, mainly sulfonylureas. Glimepiride is a recent sulfonylurea that exerts antidiabetic action by stimulating insulin secretion from pancreatic beta cells *(8,10,11)*.

Table 3
Comparison of Responder Rates (n = 263)

		Greece		Italy		Spain		Total		c^2test
		Nonresp	Responder	Nonresp	Responder	Nonresp	Responder	Nonresp	Responder	p-value[a]
Breakfast	*n*	3	8	15	32	6	25	24	65	0.091
	%	27.27	72.73	31.91	68.09	19.35	80.65	26.97	73.03	
Lunch	*n*	2	8	7	37	12	18	21	63	
	%	20.00	80.00	15.91	84.09	40.00	60.00	25.0	75.0	
Dinner	*n*	1	11	5	39	7	27	13	77	
	%	8.33	91.67	11.36	88.64	20.59	79.41	14.44	85.56	
Total	*n*	6	27	27	108	25	70	58	205	
	%	18.18	81.82	20.0	80.0	26.32	73.68	22.05	77.95	

[a]Mantel–Haenzsel test for differences between treatments, stratified by country.

Table 4
Descriptive Statistics for HbA_{1c} (%) Measured on Admission (Visit 1), After Titration (Visit 3) and at Endpoint (visit ≤9)

Variable	Number of patients	Admission		Endpoint		Change	
		Mean	SD	Mean	SD	Mean	SD
HbA_{1c} (%)							
Breakfast	74	7.86	1.012	7.75	0.990	–0.11	0.893
Lunch	76	7.89	0.972	7.78	1.165	–0.11	1.073
Dinner	80	7.78	1.349	7.60	1.131	–0.18	1.164
		After Titration		Endpoint		Change	
HbA_{1c} (%)							
Breakfast	73	7.75	0.949	7.72	1.003	–0.02	0.842
Lunch	75	7.73	0.938	7.76	1.162	0.03	0.846
Dinner	75	7.55	0.971	7.55	1.051	–0.00	0.871

Table 5
Descriptive Statistics for Secondary Efficacy Variables Measured after Titration (Visit 3), and at Endpoint (Visit ≤9)

Variable	Number of patients	After titration		Endpoint		Change	
		Mean	SD	Mean	SD	Mean	SD
Serum Insulin (mU/L)							
Breakfast	73	13.11	6.953	12.82	8.986	–0.29	7.199
Lunch	75	11.80	5.788	11.82	6.499	0.02	5.520
Dinner	75	13.02	6.792	12.13	6.321	–0.89	6.195
Serum C-peptide (ng/mL)							
Breakfast	74	2.01	0.840	2.05	0.996	0.04	0.685
Lunch	75	1.92	0.874	2.00	0.979	0.08	0.808
Dinner	75	1.95	0.881	1.95	0.835	–0.00	0.656
Blood glucose (mmol/L)							
Breakfast	74	8.68	1.959	9.59	2.301	0.90	2.749
Lunch	78	9.11	1.940	9.73	2.514	0.62	2.685
Dinner	76	8.66	2.008	9.66	2.255	1.00	2.683

Once-daily administration provides acceptable metabolic control for 24 h, which facilitates patient compliance *(7,8)*. However, the optimal time of day for administration of the drug has not been established.

The present study was designed to determine the best time of the day to administer a once-daily dose of Glimepiride in type 2 diabetic patients in the Mediterranean area. One of the differences between the Mediterranean diet and Anglo-Saxon diet is the distribution of the caloric intake during the day *(9)*. As it is observed in Table 2, despite of what we trained all patients to follow, according to the international recommendations, we observed that the compliance of the diet was variable between patients. However, nondifference of intake and distribution were observed between groups. Given the pharmacokinetics of Glimepiride, it is reasonable to hypothesize that optimizing metabolic control and minimizing the frequency of hypoglycemic events might depend on the time of administration.

All patients enrolled in this clinical trial were monitored to assess metabolic control and the presence of adverse events including hypoglycemia. The time of administration had no significant effect on the action of the drug, although the dinner group showed a better rate of response and a greater reduction in HbA_{1c} with fewer hypoglycemias. The differences in blood glucose levels (lowest value in the lunch group), which were less than 6 mmol/L, suggest that the center effect could be attributed to the difference in the center's sample size.

Hypoglycemia is the most relevant adverse event of sulfonylurea treatment. Several recent studies were performed to determine the frequency and causes of mild hypoglycemia with different sulfonylureas *(12,14)*. A significant inverse relationship with the duration of treatment was observed: most such episodes occurred in the first 4 yr of treatment, with lower HbA_{1c} values in the group of patients who suffered more hypoglycemias.

The severity of hypoglycemic episodes in the patients treated with Glimepiride, who had signs and symptoms of hypoglycemic, was similar in all three treatment groups. So, no changes in the frequency or intensity of hypoglycemic episodes were detected in relation to the time of the day when Glimepiride was administered.

Only a small percentage of hypoglycemias showed both symptoms and blood glucose determinations under 60 mg/dL, suggesting an advantageous profile of Glimepiride, administered once daily, in the treatment of type 2 diabetic patients in the Mediterranean area.

Conclusion

Given the differences in diet between Mediterranean countries and central and north European countries, the present trial was designed to examine whether the efficacy of Glimepiride—administered once daily—was related to the time of administration. There was no relationship between the time when Glimepiride was administered and the metabolic control achieved

Acknowledgment

To all the investigators involved in this study (in alphabetical order): *Greece*: Professor Vassilis Karamanos (Ippokration General Hospital, Athens) and Professor Nik Katsilambros (Laiko General Hospital, Athens). *Italy*: Professor Giandomenico Bompiani (Clinical Medica I, Universitá degli Studi, Palermo). Professor Riccardo Giorgino (Clinica Medica III, Universitá degli Studi, Bari), Professor Mario Mancini (Policlinico Universitario, Napoli), Professor Umberto di Mario (Policlinico Umberto I, Roma), Professor Luciano Motta (Ospedale Cannizaaro, Catanio) and Professor Riccardo Scardapane (Opsedale Miulli, Acquiaviva delle Fonti). *Spain*: Dr. Juan Ascaso (Hospital Clinico, Valencia), Dr. Ricardo Astorga (Hospital Virgen del Rocío, Sevilla), Dr. Aniceto Charro (Hospital Clínico San Carlos, Mad-rid), Dr. Antonio Jara (Hospital General Gregorio Marañón, Madrid), Dr. Manuel Puig (Hospital de la Santa Creu i Sant Pau, Barcelona), Dra. Anna Sanmarti (Hospital Germans Trias i Pujol, Badalona) and Dr. José Antonio Vázquez (Hospital de Cruces, Barakaldo). Dr. Angeline Matroos (Hoechst Marion Roussei, Hoevelaken, The Netherlands) and Miss Berta Ferreiro for secretarial help in preparing the statistical report of this study.

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