Long-Term Treatment of Type 2 Diabetic Patients with the New Oral Antidiabetic Agent Glimepiride (Amaryl®): A Double-Blind Comparison with Glibenclamide

K. E. Draeger, K. Wernicke-Panten, H.-J. Lomp, E. Schüler and R. Roßkamp

Glimepiride Multicentre Study Group, Clinical Research, Hoechst AG, Frankfurt, Germany

An international, prospective, double-blind trial compared the long-term therapeutic value of glimepiride with glibenclamide in patients with Type 2 diabetes mellitus. Patients stabilised on glibenclamide were randomised to 1 mg glimepiride (524 patients) or 2.5 mg glibenclamide (520 patients). The treatment groups were comparable at baseline with respect to age (60.2 years), body mass index (26.5 kg/m²), duration of diabetes (5.0 years) and fasting blood glucose levels (163 mg/dl [9.0 mmol/l]). Doses were increased stepwise, up to 8 mg for glimepiride (once-daily) and 20 mg for glibenclamide (> 10 mg as divided dose), until metabolic control (fasting blood glucose ≤ 150 mg/dl [8.3 mmol/l]), or maximum dose was achieved. After one year of treatment, patients entered a long-term follow-up study. Primary endpoints for evaluation of metabolic control, mean glycated haemoglobin and mean fasting blood glucose, were 8.4 % and 174 mg/dl (9.7 mmol/l) for glimepiride and 8.3 % and 168 mg/dl (9.3 mmol/l) for glibenclamide. Differences between treatment groups were not considered clinically relevant (95 % confidence intervals (– 0.05, 0.19 %) for glycated haemoglobin and (2, 11 mg/dl) [0.1, 0.6 mmol/l] for fasting blood glucose). Statistically significant lower fasting insulin and C-peptide values were observed in glimepiride patients compared with glibenclamide (differences: insulin, – 0.92 μU/ml [p = 0.04]; C-peptide, – 0.14 ng/ml [p = 0.03]). Both treatment groups showed an equivalent safety profile. Adverse events were consistent with the nature of the diabetic patient population studied. Fewer hypoglycaemic reactions occurred with glimepiride than with glibenclamide (105 versus 150 episodes). The long-term follow-up (457 patients) confirmed that glimepiride (1 – 8 mg) once daily provides equivalent metabolic control to a higher dosage (2.5 – 20.0 mg) of glibenclamide. Both treatments were well tolerated.

Key words: Type 2 (Non-Insulin Dependent) Diabetes Mellitus – Clinical Trial – Glimepiride – Glibenclamide – Glycaemic Control

Abbreviations

FBG:	Fasting blood glucose
HbA_{1c}:	Glycated haemoglobin
NIDDM:	Non-insulin-dependent diabetes mellitus

Introduction

Glimepiride (HOE 490; Amaryl®) is a new sulfonylurea which is more potent on a mg per mg basis than any sulphonyl-urea, more rapid acting than glibenclamide, with a long duration of action (2,4,8), and has a complete bioavailability (1).

The main aim of the present study was to compare the efficacy and safety of glimepiride with that of glibenclamide over an extended period of time.

Patients and Methods

The study was conducted at 22 study centres in the UK and at 27 other centres located in Europe, Asia, South Africa and South America.

Patient selection

Male and female patients with type II diabetes mellitus, aged between 40 and 80 years, were eligible to participate in the study. Patients must have been on glibenclamide for at least two months. In addition, patients were to have had a fasting blood glucose (FBG) level of ≤250 mg/dl (13.9 mmol/l) on at least two occasions before the study started.

The study specifically excluded patients with a previous history of documented oral sulfonylurea treatment failure (primary or secondary) and patients who had been treated with insulin within the 12 months prior to enrolment. Patients were also excluded if they had a history of hypersensitivity to sulfonylureas, liver or kidney damage, or gastrointestinal disorders which may have interfered with absorption of the study drugs. Other exclusion criteria included ketonuria with concurrent glycosuria, acute infection, diseases of the blood or haematopoietic organs, pregnancy and breastfeeding. Patients were not eligible to participate if they were receiving concomitant medications which may have interacted with the hypoglycaemic action of the study drugs.

All patients gave their written informed consent to participate in the study and each study centre received local ethics committee approval.

Horm. Metab. Res. 28 (1996) 419 – 425

Study design

After a two week open run-in phase to assess eligibility, patients were randomised to treatment with either glimepiride or glibenclamide for a 12 month double-blind treatment period which comprised a titration phase of two months and a maintenance phase of 10 months.

Patients started double-blind treatment with the lowest dose of 1 mg glimepiride or 2.5 mg glibenclamide. The dose of study medication was increased one week later if satisfactory metabolic control had not been achieved (the therapeutic goal was defined as FBG ≤ 150 mg/dl [8.3 mmol/l] and less than or equal to the concentration at the beginning of the study if baseline values were lower than that defined objective). Dosage increases could have occurred earlier than one week if the patient showed metabolic deterioration or FBG increased by more than 50 mg/dl (2.8 mmol/l). Patients were taken through a maximum of six sequential dose-titration steps until the therapeutic goal or maximum dose was achieved. The dosing steps were 1, 2, 3, 4, 6 and 8 mg for glimepiride and 2.5, 5, 7.5, 10, 15 and 20 mg for glibenclamide. The dose was to be decreased in the event of an FBG value less than 70 mg/dl [3.9 mmol/l] (or any blood glucose concentration less than 50 mg/dl [2.8 mmol/l]) and/or clinical signs of hypoglycaemia.

The study medications were formulated to be indistinguishable from each other and administered once daily in the morning except for the two highest doses of glibenclamide which were given in divided doses (morning and evening). To preserve blinding of the study, in the glimepiride group placebo tablets were administered in the evening for dosing steps 5 and 6.

Patients received individual dietary recommendations from the investigator, and an individualised breakfast was provided on each examination day.

Patients attended the hospital for eligibility screening at the beginning of the two week run-in phase and then on the first day of the two month double-blind titration phase when baseline measurements were recorded. Subsequent visits were at weekly intervals for the first month, at two months, and at two monthly intervals thereafter, with the final visit at 12 months. Blood glucose (fasting and at 1 and 2 hours post-prandial) was measured at screening and at every visit thereafter. Glycated haemoglobin (HbA_{1c}) and blood lipids were measured at baseline and then at every visit from one month onwards. Insulin and C-peptide (fasting and 2 hours post-prandial) were measured at baseline, six months and 12 months.

Patients who were eligible to continue at the end of 12 months (adequate metabolic control was achieved and patient and physician decided to proceed with the study) were followed-up for a prolonged double-blind treatment period as part of a separate extended follow-up study.

Safety assessments

Safety and tolerability of the study medications was assessed primarily from adverse events spontaneously reported by the patients and from measuring routine haematological and biochemical laboratory variables. In addition, patients underwent a physical examination (including measurement of blood pressure) at the beginning of the trial and after 12 months. Bodyweight was determined at baseline, at one month and every two months during the maintenance phase, and body mass index (BMI) was calculated.

Hypoglycaemia was defined as hypoglycaemic symptoms reported by the patient, a fasting blood glucose of ≤ 70 mg/dl (3.9 mmol/l), or a blood glucose of ≤ 50 mg/dl [2.8 mmol/l].

Statistics

Two primary efficacy variables were defined: the difference from baseline in mean values of HbA_{1c} for the maintenance phase (2–12 months with the first assessment at 4 months), and the mean FBG values over the maintenance phase. The two treatment groups were compared for these primary variables using analysis of covariance with the baseline value used as the covariate.

A range of secondary variables included within-patient variability for fasting and 2 hour post-prandial blood glucose, visit by visit and endpoint changes from baseline in HbA_{1c}, blood glucose, insulin, C-peptide, total cholesterol and high and low density lipoprotein fractions.

In order to check the robustness of the primary per-protocol-analysis an intention-to-treat (ITT) analysis was performed for both HbA_{1c} and FBG (9).

The per-protocol population included all patients (excluding major protocol violators) who had both one baseline value and at least one value during the maintenance phase, whereas the ITT population consisted of all patients who had one baseline value and at least one post-baseline value. Missing values were replaced by linear interpolation and by the principle of last value carried forward.

Statistical evaluation of therapeutic dose range

An evaluation of the dose-response relationship was performed to determine the highest dose at which an appreciable further benefit in metabolic control was achieved with respect to reduction of FBG. To this end, the analysis determined for each patient the lowest dose level at which the mean FBG was lower or equal to the mean maintenance FBG (visit 7 to endpoint). Furthermore, to quantify the reduction in FBG gained by the titration, for each dose level a pairwise comparison with lower dosages was performed using only FBG values of those patients having that dose as their final dose.

Results

Patients

Overall, 1044 patients pre-treated with glibenclamide were randomised to treatment, 524 patients to glimepiride and 520 to glibenclamide. The treatment groups were well matched for baseline characteristics (Table **1**). Although there was a statistically significant difference between treatment groups in age of onset of diabetes, the magnitude of this difference (one year) was small and did not have any impact on the results of the primary analysis.

Table 1 Patient characteristics at baseline

Characteristic	Glibenclamide	Glimepiride	Total
Number randomised	520	524	1044
Sex (n)			
Male	340	325	665
Female	180	199	379
Age (years)			
Mean	60.7	59.7	60.2
Range	26 – 81	27 – 81	26 – 81
BMI (kg/m^2)			
Mean	26.5	26.5	26.5
Range	18 – 39	18 – 40	18 – 40
FBG (mg/dl) [mmol/l]			
Mean	163 [9.0]	162 [9.0]	163 [9.0]
Range	40 – 353 [2.2 – 19.6]	63 – 357 [3.5 – 19.8]	40 – 357 [2.2 – 19.8]
HbA_{1c} (%)			
Mean	8.1	8.1	8.1
Range	5.1 – 13.1	5.5 – 12.9	5.1 – 13.1
Duration of diabetes (years)			
Median	5.0	5.0	5.0
Range	0 – 36	0 – 40	0 – 40
Age at onset (years)			
Median	54	53	54
Range	20 – 77	21 – 77	20 – 77
Duration of previous oral treatment (years)			
Median	4.0	3.6	3.8
Range	0.3 – 27	0.2 – 41	0.2 – 41

BMI = body mass index; FBG = fasting blood glucose; HbA_{1c} = glycated haemoglobin

The study population comprised 74% white patients with 26% black, Asian or of other race. Diabetic complications, such as retinopathy, neuropathy, peripheral vascular disease or elevated diastolic blood pressure, were recorded in 40% of patients. Concomitant medications were taken by 69% of patients, most commonly cardiovascular medications, central nervous system depressants, antirheumatics and anti-infectives. A similar proportion of patients (68%) had previous or concomitant diseases. There were no relevant differences between the treatment groups for any of these background characteristics.

Treatment

Of the 1044 patients randomised to treatment, 398 (76%) glimepiride patients and 418 (80%) glibenclamide patients completed the 12-month study. The most common reason in each treatment group for discontinuation was lack of efficacy.

Patients were titrated through the six dose levels until metabolic control or maximum dose was achieved. During the maintenance phase, the majority of patients (56%) remained at the same dose level throughout the study period, but 42% of patients had their dose increased and a small proportion (2%) were changed to a lower dose. The proportion and pattern of changes which occurred during the maintenance phase were similar for the two treatment groups.

There were statistically significant differences between the treatment groups in dose distribution at several visits including endpoint. At endpoint, there were more glimepiride (51%) than glibenclamide (42%) patients at dose level 6 and more glibenclamide than glimepiride patients at dose levels 1 and 5 (Fig. **1**). Approximately 20% of patients in each treatment group remained at the first dosage level for the entire study.

Assessment of metabolic control

Main analyses of metabolic control

HbA_{1c} was slightly higher (approximately 0.3%) during the maintenance phase than at baseline in both treatment groups. Although the mean increase was higher for glimepiride compared with glibenclamide (Table **2**), the difference between treatment groups (0.07%) was not statistically significant ($p = 0.25$). The treatments were therefore considered therapeutically equivalent with respect to HbA_{1c} values. The intention-to-treat analysis confirmed the findings of the per-protocol analysis.

FBG values during the maintenance phase were also slightly higher (approximately 9 to 16 mg/dl; [0.5 to 0.9 mmol/l] in both treatment groups compared with baseline values. An overall lower mean value was observed with glibenclamide compared with glimepiride (Table **3**), and the difference between treatments (7 mg/dl [0.4 mmol/l]) was statistically significant ($p = 0.005$). This small difference in FBG is considered to be of no clinical relevance. The treatments were therefore considered therapeutically equivalent also with respect to FBG values. Again, the intention-to-treat analysis confirmed the findings of the per-protocol analysis.

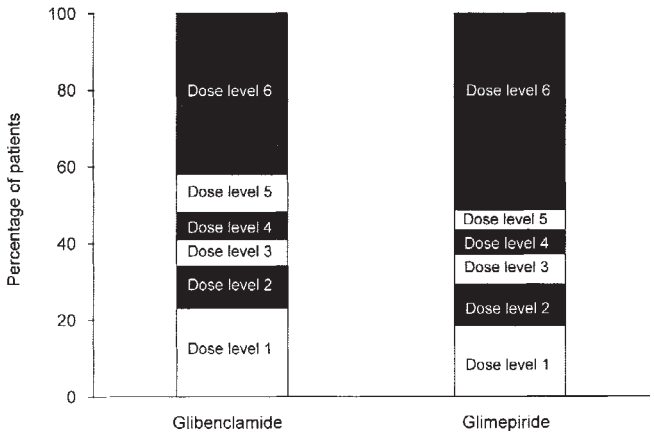

Fig. 1 The percentage of patients in the glimepiride and glibenclamide treatment groups at each dose level at endpoint.

Table 2 Changes in glycated haemoglobin (per-protocol analysis).

	Glibenclamide (n = 451)	Glimepiride (n = 455)
Mean value at baseline (%)	7.80	8.03
Mean value over maintenance phase[a] (%)	8.32	8.39
Mean change[a] (%) (maintenance phase – baseline)	0.31	0.38
Mean difference[a] (%) (glimepiride – glibenclamide)	0.07	
p value	0.25	
95 % confidence interval (%)	– 0.05, 0.19	

[a] mean values adjusted for baseline differences

Supporting analyses

The visit by visit and endpoint analyses confirmed the conclusions of the primary analyses. The HbA_{1c} and FBG values were slightly lower in the glibenclamide group and the maximum difference compared to glimepiride being 0.1 % HbA_{1c} (visit 5) and 9 mg/dl (0.5 mmol/l) FBG (visit 4) (see Figs. **2** and **3**).

Within-patient variability of blood glucose levels was assessed from fasting levels and from 2 hour post-prandial levels. The variability at each time point was almost identical for both treatment groups (about 18 mg/dl [1.0 mmol/l] for FBG and 29 mg/dl [1.6 mmol/l] for the 2 hour post-prandial level blood glucose).

Table 3 Changes in fasting blood glucose levels (per-protocol analysis).

	Glibenclamide (n = 453)	Glimepiride (n = 465)
Mean value at baseline (mg/dl) [mmol/l]	159 [8.8]	159 [8.8]
Mean value during maintenance phase[a] (mg/dl) [mmol/l]	168 [9.3]	174 [9.7]
Mean change[a] (mg/dl) [mmol/l] (maintenance phase – baseline)	9 [0.5]	16 [0.9]
Mean difference[a] (mg/dl) [mmol/l] (glimepiride – glibenclamide)	7 [0.4]	
p value	0.005	
95 % confidence interval (mg/dl) [mmol/l]	2, 11 [0.1, 0.6]	

[a] mean values adjusted for baseline differences

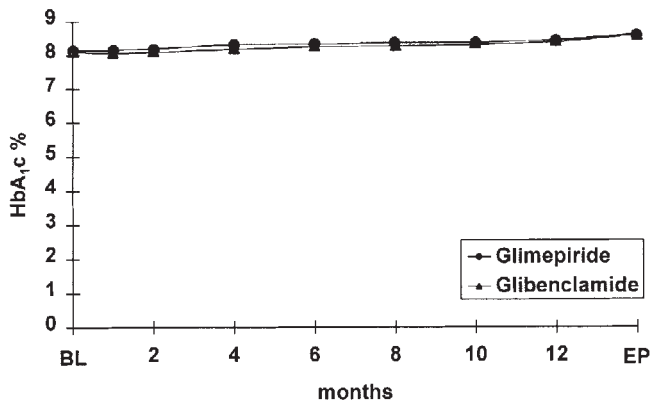

Fig. 2 Mean HbA_{1c} (%) levels at each visit over 12 months for the glimepiride (●) and glibenclamide (▲) treatment groups. BL = baseline; EP = endpint

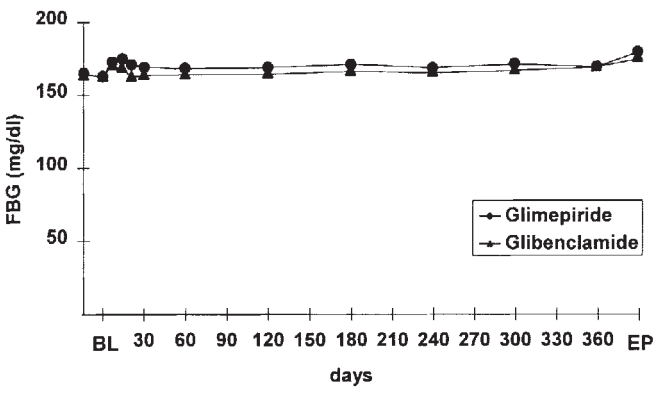

Fig. 3 Mean fasting blood glucose (mg/dl) at each visit over 12 months for the glimepiride (●) and glibenclamide (▲) treatment groups. BL = baseline; EP = endpoint

Table 4 Changes in fasting insulin levels.

	Glibenclamide (n = 425)	Glimepiride (n = 429)
Median value at baseline (μU/ml)	15.62	15.29
Median value at endpoint (μU/ml)	17.77	17.47
Median change (μU/ml) (endpoint – baseline)	2.22	1.27
Median difference (μU/ml) (glimepiride – glibenclamide)	– 0.92	
p value	0.041	

Table 5 Changes in fasting C-peptide levels.

	Glibenclamide (n = 417)	Glimepiride (n = 429)
Median value at baseline (ng/ml)	1.98	2.00
Median value at endpoint (ng/ml)	2.43	2.38
Median change (ng/ml) (endpoint – baseline)	0.47	0.28
Median difference (ng/ml) (glimepiride – glibenclamide)	– 0.14	
p value	0.034	

Other metabolic measures

Lower values of fasting insulin were observed in the glimepiride group compared with glibenclamide (Table **4**). The median change from baseline to patient endpoint for all patients was lower for glimepiride (1.27 μU/ml) than glibenclamide (2.22 μU/ml) and the median difference of 0.92 μU/ml was statistically significant (p = 0.041).

A similar difference was observed for C-peptide levels (Table **5**). The median change from baseline to endpoint was 0.28 ng/ml for glimepiride and 0.47 ng/ml for glibenclamide, median difference 0.14 ng/ml (p = 0.034).

In both treatment groups there were essentially no changes in blood lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) or BMI between baseline and endpoint.

Evaluation of dose level

The above analyses do not take into account the different dose levels that patients may have been receiving. As expected, patients receiving the higher dose levels at endpoint were generally those patiens with poorer metabolic control, both at baseline and at endpoint. For example, HbA_{1c} values for patients who ended the trial at dose level 1 were approximately 6.9% at baseline and 7.1% at endpoint; corresponding values for patients who ended the trial at dose level 6 were 8.8% at baseline and 9.5% at endpoint.

Dose-response relationship analyses were performed to examine the highest dose level at which an additional gain in metabolic control was achieved. These analyses revealed that although some patients benefited from titration up to the highest dose level, most patients in either treatment group did not achieve better metabolic control from titration to the highest dose levels. For example, more than 85% of the patients who completed the study at dose level 6 had already achieved their individual average metabolic control at lower dose levels during the maintenance phase. The pairwise comparison of dose levels confirmed the results of the lowest dose-to-event analyses. Patients on end-dose level 6 did not show a general decrease of FBG while being titrated. On the other hand, patients ending the study on one of dose levels 2 to 5 showed a median decrease of about 10 to 20 mg/dl (0.6 to 1.1 mmol/l) FBG resulting from the last titration step to their end dose.

Safety

In general, the pattern and frequency of adverse events reported during the study was consistent with the age and diabetic history of the patient population. Overall, a total of 320 adverse events considered to be at least possibly related to study treatment were reported from a total of 190 patients: 90 patients (17%) in the glimepiride group and 100 patients (19%) in the glibenclamide group. Serious adverse events considered to be drug-related by the investigator were reported from five glimepiride patients and eight glibenclamide patients. None of the 16 deaths (11 glimepiride, 5 glibenclamide) were considered to be related to the study mediction. The reasons for death during glimepiride treatment were: congestive heart failure (1), myocardial infarct (3), myocardial ischemia (1), liver carcinoma (1), prostatic carcinoma (1), apnea (CO intoxication) (1). The reasons for death during glibenclamide treatment were: congestive heart failure (1), myocardial infarct (2), carcinoma (1), carcinoma of kidney (1).

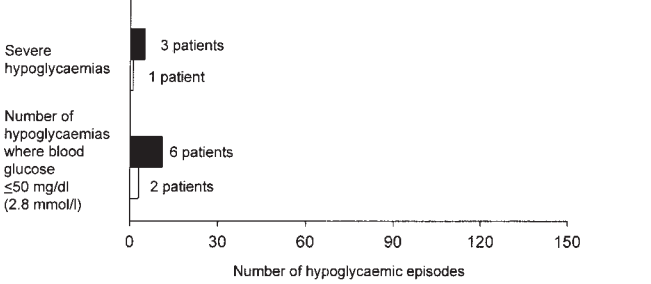

Fig. 4 Numbers of hypoglycaemic episodes in the glimepiride (□) and glibenclamide (■) treatment groups.

Fewer episodes of hypoglycaemia were observed in the glimepiride group compared with glibenclamide. Overall, 74 (14%) patients in the glibenclamide group experienced 150 episodes of hypoglycaemia compared with 60 (11%) patients in the glimepiride group who experienced 105 episodes (Fig. **4**). Three episodes of hypoglycaemia in the glibenclamide group compared with one in the glimepiride group were reported as being severe (patients needed help). Blood glucose decreased to ≤ 50 mg/dl (2.8 mmol/l) on two occasions (in two patients)

Table 6 Patient characteristics at baseline of follow-up study.

Characteristic	Glibenclamide	Glimepiride
Number randomised	229	228
Sex (n)		
Male	152	144
Female	77	84
Age (years)		
Mean	62.2	61.4
Range	41 – 82	41 – 79
BMI (kg/m²)		
Mean	26.78	26.93
Range	18.9 – 37.7	18.3 – 34.7
FBG (mg/dl) [mmol/l]		
Mean	157 [8.7]	158 [8.8]
Range	71 – 297 [3.9 – 16.4]	70 – 321 [3.9 – 17.8]
HbA_{1c} (%)		
Mean	8.0	8.0
Range	5.3 – 13.5	5.7 – 13.6

BMI = body mass index; FBG = fasting blood glucose; HbA1c = glycated haemoglobin

in the glimepiride group compared with 11 occasions (in six patients) in the glibenclamide group.

In terms of laboratory findings, there was little overall change between the first and last measurements for most variables. Of the few variables which did show a statistically significant change, none was considered to be of any clinical relevance.

Results from the follow-up study

At the end of the 12-month study, 457 patients (228 glimepiride, 229 glibenclamide) continued with their study medication and participated in an extended follow-up study. The remaining patients did not enrol for personal reasons, e.g. they did not want to proceed in a clinical trial, or due to the recommendations of the investigator, e.g. transfer to other medications such as insulin. Characteristics of the patients are summarised in Table **6**. The mean duration of follow-up varied considerably between patients (mean 251 days; range 7 to 526 days). The majority of patients (184 glimepiride, 166 glibenclamide) maintained the same dose level for the entire follow-up period.

Mean FBG values (measured every three months) were similar between the treatment groups. There were no statistically significant differences between the treatment groups at any visit and there were also no statistically significant differences within or between treatment groups for changes from baseline at any visit. Similarly, mean HbA_{1c} values (measured every six months) were also almost identical for the two treatment grous. There were no significant differences in the changes from baseline at any visit between the treatment groups.

The pattern of adverse events reported during the study was consistent with the age and diabetic history of the patient population. Treatment-related adverse events were reported by 18 glimepiride patients (25 events) and 12 glibenclamide patients (17 events). Hypoglycaemic events were reported for seven glimepiride patients (seven cases) and nine glibenclamide patients (10 cases); none was classed as being severe.

Discussioon

In order to compare the therapeutic effects of the two compounds, the study needed to show whether once daily glimepiride could confer average metabolic control equivalent to that provided by the standard treatment. All of the comparisons of metabolic control indicated that the two treatment groups were therapeutically equivalent. However, it is important to note that patients receiving glimepiride maintained metabolic control with significantly lower fasting insulin and C-peptide values compared with those receiving glibenclamide. This may be a potentially important finding since it has been suggested that hyperinsulinaemia can induce hypertension and/or late complications (12).

A slight deterioration of blood glucose control was observed after the one year treatment period (glimepiride: HbA_{1c} + 0.44% and FBG + 10 mg/dl [0.6 mmol/l]; glibenclamide: Hba_{1c} + 0.37% and FBG + 7 mg/dl [0.4 mmol/l]). The magnitude of this deterioration is in keeping with published data (6). This indicates that progression of the disease is similar under both drugs.

The majority of patients was well controlled with the lower dose levels, whereas most patients at the highest dose level (8 mg glimepiride, 20 mg glibenclamide) had already reached their individual optimal metabolic control with lower doses and did not benefit from titration to the highest dose level. This is in agreement with the results of a placebo-controlled trial where there was no significant difference between 4 and 8 mg glimepiride although some patients may have had a benefit (11). It also concurs with data from a clamp study in which steady state glibenclamide concentrations were achieved by infusion (5) suggesting that about 10 mg of glibenclamide yield the maximum effect.

In the present study, blood lipids, body weight and blood pressure, showed no clinically relevant differences, either from baseline to endpoint or between treatment groups.

Both treatments showed a good safety profile, as it is well known for the sulphonylurea class of compounds. None of the events, including those classed as serious, was unexpected considering the age and diabetic history of the patient population.

Fewer glimepiride patients (11%) experienced an episode of hypoglycaemia than did glibenclamide patients (14%). The risk of hypoglycaemia generally increases with age, poor nutrition, impaired renal function and in patients on multiple drug therapy (3,7). However, the true incidence of hypoglycaemia is difficult to estimate since it varies considerably between studies due to the uncertainty of the subjective patient reporting.

Results from the long-term follow-up study confirmed the findings of the initial 12-month study, thereby emphasising the long-term safety and efficacy of glimepiride in comparison with glibenclamide.

Summing up, results from the present trial indicate that glimepiride offers the same strong blood-glucose lowering effect of glibenclamide. Metabolic control is achieved with a lower dose to be given only once daily which promises to improve compliance. Whereas general tolerability is similar to that of standard therapy, the lower incidence of hypoglycaemia with glimepiride has to be considered a distinct advantage.

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Requests for reprints should be addressed to:

K. E. Draeger
Clinical Research H840
Hoechst AG
D-65926 Frankfurt
Germany