Summary

Objectives: In type 2 diabetes, the primary and secondary prevention of long-term micro- and macrovascular complications requires a control of blood glucose levels 24 hours a day. The present study was undertaken to assess the effect of a new formulation of gliclazide administered once daily, gliclazide modified release (1), on plasma glucose levels over 24 hours.

Material and Methods: In 21 type 2 diabetic patients previously treated by diet alone or oral antidiabetic agents, glycemic profile (8 am, 10 am, 12 am, 2 pm, 5 pm, 8 pm, 10 pm, 3 am and 8 am), overall glycemic control, acceptability, and compliance with treatment were assessed before and after a 10-week treatment with gliclazide modified release, (30-60 mg), given once daily at breakfast.

Results: The results indicate a significant decrease in plasma glucose levels at all points of the cycle. Mean plasma glucose levels over 24 hours and mean plasma glucose levels during the fasting and the postprandial periods were significantly improved after treatment. In previous drug-naive patients, decrease in HbA1C was observed (1.0 ± 1.1%, P = 0.022). The acceptability was good, with no hypoglycemic events, and a high compliance with treatment was also observed.

Conclusion: We can therefore conclude that gliclazide modified release, given once daily at breakfast, is effective over 24 hours in reducing plasma glucose levels in type 2 diabetes. This once-daily administration should lead to an optimal patient compliance with treatment.

Key-words: type 2 diabetes mellitus, treatment, sulfonylurea, gliclazide modified release, compliance, glycemic profile, HbA1C.

Résumé

Objectifs : Chez les patients atteints de diabète de type 2, la prévention primaire et secondaire des complications chroniques micro- et macrovasculaires nécessite un bon équilibre de la glycémie durant tout le nycthémère. La présente étude a été réalisée dans le but de vérifier l’effet d’une nouvelle formulation du gliclazide administrée une seule fois par jour, le gliclazide à libération modifiée, sur le cycle glycémique de 24 heures.

Matériel et Méthodes : Chez 21 diabétiques de type 2 préalablement traités par régime seul, ou associé à des antidiabétiques oraux, le profil glycémique (8 h, 10 h, 12 h, 14 h, 17 h, 20 h, 22 h, 3 h et 8 h), l’équilibre glycémique global, la tolérance, et l’observance au traitement, ont été étudiés avant puis après 10 semaines de traitement par gliclazide à libération modifiée, (30-60 mg), avec une seule administration orale quotidienne au petit déjeuner.

Résultats : Les résultats indiquent une réduction significative de la glycémie à chacun des temps du cycle nycthéméral. La glycémie moyenne sur 24 heures et durant les périodes à jeun et les périodes post-prandiales a été significativement améliorée. Chez les patients précédemment traités par régime seul, la diminution de l’HbA1C a été de 1,0 ± 1,1 % (P = 0,022). La tolérance a été bonne, sans incident hypoglycémique et l’observance a été élevée.

Conclusion : Ces résultats permettent de conclure que le gliclazide à libération modifiée, une prise par jour au petit déjeuner, abaissa la glycémie pendant toute la durée du nycthémère. La prise unique quotidienne devrait permettre une observance optimale.

Mots-clés : diabète de type 2, traitement, sulfonylurée, gliclazide à libération modifiée, observance, cycle glycémique, HbA1C.
The results of intervention studies, such as the UKPDS [1] and the Steno type 2 diabetes study [2], have provided strong evidence of the importance of achieving normal or near-normal HbA1c levels in preventing diabetic complications. Many studies have emphasized the need to control blood glucose levels both in the fasting and the postprandial state [3]. Another aim is improving compliance with antidiabetic treatment, which has been shown to be poor in type 2 diabetes [4], like in other chronic diseases [5]. Gliclazide modified release (1), is a new formulation of type 2 diabetes treatment, which has been shown to be poor in both in the fasting and the postprandial state [3]. Another aim is improving compliance with antidiabetic treatment, which has been shown to be poor in type 2 diabetes [4], like in other chronic diseases [5]. Gliclazide modified release (1), is a new formulation of type 2 diabetes treatment. The aim of the development of this new formulation was to closely relate gliclazide release to the 24-hour glycemic profile observed in type 2 diabetes [6]. Pharmacokinetic studies with this formulation show that during chronic treatment of type 2 diabetic patients, gliclazide plasma concentrations increase progressively after oral administration at breakfast. A relative plateau is observed between 3 and 12 hours, with a tmax of around 6 hours. The concentrations then decrease gradually during the rest of the 24 hours [7].

The aim of the present study was to confirm in a medium-term duration study that this pharmacokinetic profile provides effective 24-hour plasma glucose levels with gliclazide modified release, given once daily at breakfast.

### PATIENTS AND METHODS

**Patients** – Type 2 diabetic patients, defined according to ADA and WHO criteria [8, 9], were included in a single-center, open-label, 10-week clinical trial with gliclazide modified release. The study was performed at the Clinical Research Unit of Focus (Germany). Selection criteria were age between 35 and 75 years, body mass index (BMI) between 24 and 32 kg/m² and treatment for at least 3 months by diet alone or diet with an α-glucosidase inhibitor and/or a sulfonylurea at less than half the recommended maximal dosage for the latter. Inclusion criteria included glycated haemoglobin (HbA1c) levels between 6% and 9%, fasting plasma glucose (FPG) levels between 7.8 and 15 mmol/L and compliance of more than 80% after a 2-week placebo run-in period. Patients with type 1 diabetes, renal or liver failure, cardiovascular or endocrine diseases, or drug or alcohol abuse were excluded, as well as women of child-bearing potential with no contraception, and pregnant or breastfeeding women. The study protocol was approved by the Ethics Committee of the General Medical Council of Nordrhein. All patients gave written informed consent. The study was conducted according to principles of Good Clinical Practice and the Declaration of Helsinki.

**Study design** – At day 1, patients started treatment with the lowest dose of gliclazide modified release 30 mg once daily. After 2 weeks, the dosage was increased to 60 mg/day if FPG was not < 7.8 mmol/L.

A 24-hour glycemic profile was recorded before (day 0) and after the treatment period (day 70) according to the same protocol. Patients were hospitalized from the evening prior to this test to the morning afterwards. During the hospitalization, the patient did not take any food other than the standard meals served at 8 pm, 8 am, 12 am, and 8 pm (50% carbohydrates, 30% lipids, and 20% proteins and a total calorie intake of 650 kcal for breakfast and dinner, and 720 kcal for lunch.). Blood samples for blood glucose assay were taken at 8 am (just before drug intake), 10 am, 12 am, 2 pm, 5 pm, 8 pm, 10 pm, 3 am and 8 am. Five samples (8 am, 12 am, 5 pm, 8 pm, and 3 am) were representative of the fasting state. Three samples (10 am, 2 pm, and 10 pm) corresponded to the postprandial state.

The patients were asked to return all treatment boxes, blisters and remaining tablets during the visits. Compliance index was calculated as the ratio of the actual number of tablets taken to the number of tablets prescribed.

All assays were performed in the Clinical Research Unit of Focus. Plasma glucose was assessed by the enzymatic method, and HbA1c by HPLC.

The activity analysis was performed on all included patients who had an evaluation under treatment. The primary activity criterion was the 24-hour glycemic profile, expressed as mean AUC over 24 hours, mean 24-h plasma glucose and mean value at each time; the secondary criterion was HbA1c. Changes over time from D0 to D70 were described for all variables. A two-tailed Student t test (α = 0.05) for paired samples was performed as a complementary analysis on the change (D70-D0) for the primary and secondary criteria. Moreover, a two-tailed Student t test was also performed on mean values at each time of the glycemic profile (from 8 am to 3 am), using a Bonferroni correction for the type I error (α).

### RESULTS

**Patients characteristics** – A total of 22 patients were included in the study. One patient withdrew at day 42, due to an adverse event not related to treatment. This patient had no glycemic profile evaluation under treatment and was thus not included in the activity analysis. The characteristics of the 22 patients are outlined in Table I. Of the 21 patients included in the activity analysis, 9 had a BMI ≥ 28 kg/m². Nine patients were

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(1) Diamicron MR, Laboratoires Servier, Neuilly sur Seine, France.
previously on diet alone and 12 were treated by oral antidiabetic agents (11 on monotherapy: 8 with another sulfonylurea, 3 with an α glucosidase inhibitor, and 1 on two-drug therapy). From day 1 to day 14, all the patients received 30 mg of gliclazide modified release once daily. At day 14, the dosage was maintained in 9 patients (3 patients previously on diet alone, and 5 patients on oral antidiabetic agents, 1 patient being withdrawn as described above). Dosage was increased to 60 mg/day in 13 patients (6 patients previously on diet alone, and 7 patients on oral antidiabetic agents).

Glycemic control

Plasma glucose levels over 24 hours – After 70 days of treatment with gliclazide modified release, a significant decrease in mean plasma glucose levels was observed at each time point in the 24-hour evaluation (Fig. 1). Notably, mean FPG (8 am) significantly decreased from 10.0 ± 1.9 mmol/L to 7.6 ± 1.0 mmol/L (−2.3 ± 1.8 mmol/L, P < 0.001). Overall, a 27% decrease in mean plasma glucose levels over 24 hours and in the area under the curve of plasma glucose levels was observed (both P < 0.001) (Table II).

A significant decrease in mean plasma glucose levels was observed in both the fasting state (8 am, 12 am, 5 pm, 8 pm, and 3 am) (−2.63 mmol/L, P < 0.001), and in the postprandial state (10 am, 2 pm, 10 pm) (−3.03 mmol/L, P < 0.001) (Table II). On average, the decrease in plasma glucose levels was 3.00 mmol/L during day time (from 10 am to 8 pm) and 2.45 mmol/L during night time (from 10 pm to 8 am).

Glycemic control during the 10-week follow-up – In the whole group, mean HbA1C levels did not significantly change between day 0 (7.3 ± 1.0%) and day 70 (6.9 ± 0.7%) (−0.4%, P = 0.079). In previous drug-naive patients, a significant decrease of 1.0 ± 1.1% (P = 0.022) in HbA1C levels was observed (7.8 ± 1.4% at day 0 and 6.8 ± 0.5% at day 70). In patients switched from another oral antidiabetic agent, HbA1C at inclusion after 2-week wash-out mainly reflected the effect of previous treatment, and remained stable on gliclazide MR (6.9 ± 0.5% at day 0 and 6.9 ± 0.8% at day 70). During the 10-week treatment period, mean compliance index was 100.3 ± 2.5%

Acceptability

During the study, the tolerance of the drug was good. No hypoglycemic event, either mild or severe, was reported.

DISCUSSION

This study shows that treatment with gliclazide modified release given once daily during 10 weeks provides 24-hour glycemic control in type 2 diabetic patients. The results show a decrease in plasma glucose levels in the fasting state as well as in the postprandial state. Glycemic control, as assessed by HbA1C, was improved in previous drug-naive patients and maintained in patients switched from another oral antidiabetic agent. The acceptability of the drug was good, no hypoglycemic event was reported in this population with HbA1C already close to 7% at baseline. In these patients at a rather early stage of the disease, titration was limited to 60 mg daily as a maximal dosage (full dose range for gliclazide modified release is 30-120 mg daily). Compliance was high, the compliance index being nearly 100% in all cases.

Recent data from prospective studies, as the UK-PDS [1] and the Steno type 2 diabetes study [2], have
provided evidence of the role of an optimal glycemic control in the primary and the secondary prevention of long-term complications in type 2 diabetes mellitus. Thus, the main goal in treating these patients is to control plasma glucose levels 24 hours a day, in order to normalize (or near-normalize) HbA1c levels. Three points should be addressed to achieve this goal. The first is obtaining an optimal glycemic control in both the fasting and the postprandial state. This is mandatory to reduce HbA1c levels to normal or near-normal levels [3]. In type 2 diabetic patients treated with regular gliclazide (80 mg formulation), there is a better correlation between HbA1c levels and postprandial and evening plasma glucose levels than with morning fasting plasma glucose levels [10], as shown with other sulfonylureas [11]. The second point is the acceptability of the treatment. It is essential to use drugs with no, or at least the lowest, side effects. In this context, gliclazide modified release is safe, with no or very few minor hypoglycemic events. This has been shown in a large long-term study, notably in elderly type 2 diabetic patients [12]. In this multicenter controlled study, HbA1c levels were similar in patients treated with gliclazide modified release and with the regular formulation of gliclazide. A mean 0.9% decrease in HbA1c levels was observed in drug-naive patients after a 10-month follow-up. A low frequency of hypoglycemic minor events (no severe hypoglycemia) was reported (1.2/100 patients.month). Whether this low frequency is related to the rapid dissociation of gliclazide from the sulfonylurea receptor SUR on the β-cell membrane, is to be confirmed [13, 14]. The third point is the compliance of type 2 diabetic patients with treatment. As in other chronic diseases [5, 15, 16], compliance with treatment is pivotal in type 2 diabetes, and is often not optimal [4, 17]. The choice of a drug formulation with a once-daily dosing regimen may lead to a better compliance. In a study carried out in type 2 diabetic patients, compliance was nearly 100% with a once-daily dosing regimen, much higher than that observed with two (83%), or with three times daily (66%) dosing regimens [4]. Other studies have shown that the greater the number of daily doses, the lower the compliance [18]. Moreover, the switch from a multiple to a once-daily dosing regimen has been proven to be effective in improving compliance [19]. This is particularly important in polycladicated patients, such as type 2 diabetic patients.

In conclusion, after medium-term treatment (10 weeks) of type 2 diabetic patients with gliclazide modified release given once-daily, the glycemic profile was improved over 24 hours. There was a clear decrease in mean plasma glucose levels at all times of the day, both in the fasting and the postprandial states. In drug naive patients, a significant decrease of 1% in mean HbA1c was observed. No hypoglycemic event was observed. Finally, compliance was high, reaching nearly 100%, as previously observed in compliance studies performed with once daily regimen treatments. Thus, the new formulation of gliclazide given once daily at breakfast is safe and effective in reducing plasma glucose 24 hours a day and HbA1c levels, and should improve patient compliance with treatment.

### Table II. 24-hour glycemic profile after 70 days of treatment with gliclazide modified release in 21 type 2 diabetic patients (results expressed as mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 70</th>
<th>Day 70-Day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over 24 hours</td>
<td>10.11 ± 1.98</td>
<td>7.41 ± 1.09</td>
<td>−2.07 ± 1.69*</td>
</tr>
<tr>
<td>Fasting state</td>
<td>9.33 ± 1.82</td>
<td>6.70 ± 1.03</td>
<td>−2.63 ± 1.72*</td>
</tr>
<tr>
<td>Postprandial state</td>
<td>11.42 ± 2.45</td>
<td>8.39 ± 1.46</td>
<td>−3.03 ± 1.86*</td>
</tr>
<tr>
<td>Area under the curve</td>
<td>242.4 ± 48.5</td>
<td>177.3 ± 25.9</td>
<td>−65.1 ± 41.8*</td>
</tr>
</tbody>
</table>

* P < 0.001

### REFERENCES

GLYCEMIC PROFILE AND GLICLAZIDE MODIFIED RELEASE

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