CURRENT THERAPEUTIC RESEARCH
VOLUME 67, NUMBER 2, MARCH/APRIL 2006

Effects of Gliclazide Dose Escalation on Postprandial Hyperglycemia in Type 2 Diabetes Mellitus: A Prospective, Open-Label, Case-Controlled, Dose-Escalation Study

Poobalan Naidoo, BPharm[1]; Rambiritch Virendra, PhD[1]; and Mayet Layla, MBChB, MMedSc[2]

[1]School of Pharmacy and Pharmacology, University of KwaZulu-Natal, KwaZulu-Natal, South Africa; and [2]Diabetes Unit, Department of Medicine, Addington Hospital, KwaZulu-Natal, South Africa

ABSTRACT

Objectives: The aims of this study were to determine the effects of increasing doses of gliclazide on postprandial glucose excursions after a standardized breakfast and lunch, and to clarify the relationship between gliclazide dose and glucose response.

Methods: This prospective, open-label, case-controlled, dose-escalation study was conducted at the Addington Hospital Diabetes Clinic, eThekwini/Durban, KwaZulu-Natal, South Africa. Male and female patients aged ≥18 years with type 2 diabetes mellitus (DM) and postprandial hyperglycemia (2-hour postprandial blood glucose [$PPBG_{2\ h}$] level, ≥11.1 mmol/L [≥200 mg/dL]) and receiving an oral hypoglycemic agent were eligible. After a 1-week washout period during which patients were asked to discontinue treatment with all oral hypoglycemic agents, baseline glycemic measurements were performed (fasting blood glucose, $PPBG_{2\ h}$, 6-hour postprandial blood glucose [$PPBG_{6\ h}$], mean blood glucose [MBG], plasma insulin, fasting serum fructosamine, and glycosylated hemoglobin). All patients subsequently received 2 weeks of oral treatment with each of 3 doses of gliclazide: 40, 80, and 160 mg/d. Glycemic parameters were measured at the end of each dosing interval. Adverse-effect monitoring included direct reporting of untoward effects to the resident medical practitioner, clinical examination, monitoring of home blood glucose records, hematology, and liver and kidney function tests. Compliance was assessed using pill counts, examination of diary entries, and patient interview.

Results: Thirty-three patients were screened; 14 entered the dose-escalation phase. Thirteen patients completed the study (7 women, 6 men; mean [SD] age, 52.0 [11.1] years); 1 was withdrawn because of poor compliance. Dose escalation from 40 to 80 mg/d was associated with a significant change only in MBG (mean [SD], 11.3 [4.2] vs 10.0 [3.9] mmol/L [203.6 (75.7) vs 180.1 (70.3) mg/dL];

Accepted for publication February 9, 2006.
doi:10.1016/j.curtheres.2006.04.001
0011-393X/06/$19.00

$P < 0.001$). Dose escalation from 80 to 160 mg/d was associated with a significant change only in $PPBG_{6\,h}$ (9.5 [4.2] vs 10.3 [4.1] mmol/L [171.1 (75.7) vs 185.6 (73.9) mg/dL]; $P = 0.018$). No other significant changes in glycemic parameters between doses were found throughout the treatment period. No adverse effects were reported.

Conclusions: In this small study of gliclazide dose escalation in patients with type 2 DM and postprandial hyperglycemia, gliclazide 80 mg/d was associated with a reduction in postprandial hyperglycemia. Dose escalation from 80 to 160 mg/d was not found to be associated with additional clinical benefit. Based on these results, we recommend that gliclazide dose escalation to the maximum dose recommended by the manufacturer be guided by measures of glycemia. All doses were well tolerated. (*Curr Ther Res Clin Exp.* 2006;67:81–102)

Key words: type 2 diabetes mellitus, oral antidiabetic agents, oral hypoglycemic agents, gliclazide, postprandial hyperglycemia, sulfonylureas.

INTRODUCTION

The Diabetes Control and Complications Trial[1] and the United Kingdom Prospective Diabetes Study[2] found the benefits of blood glucose control in types 1 and 2 diabetes mellitus (DM), respectively. The findings of these landmark studies have since entrenched glucose levels as a surrogate biochemical marker to predict clinical outcomes in patients with type 1 or 2 DM.

Following the findings of those 2 trials, clinicians have focused the management of DM on the regulation of blood glucose (ie, attaining near-normoglycemia [fasting blood glucose (FBG) level, 4.0–6.0 mmol/L (72.1–108.1 mg/dL)]). Clinicians commonly base the pharmacotherapy of hyperglycemia on the objective parameters of FBG, fructosamine, and glycosylated hemoglobin (HbA_{1c}).

However, increasing evidence supports and emphasizes the importance of targeting postprandial hyperglycemia (2-hour postprandial blood glucose [$PPBG_{2\,h}$] level, 2 hours after a meal, ≥11.1 mmol/L [≥200 mg/dL]).[3] Postprandial blood glucose (PPBG) levels have been reported to be better predictors of glycemic control and to correlate better with HbA_{1c} compared with FBG.[4] In a review of literature concerning elevated PPBG as a risk factor for cardiovascular disease in patients with type 2 DM, Bonora and Muggeo[5] concluded that postprandial hyperglycemia, even in the absence of fasting hyperglycemia, was a risk factor for ischemic heart disease. In a prospective, randomized, controlled study of blood glucose monitoring in pregnant women with type 1 DM in northern Ireland, Manderson et al[6] found that PPBG monitoring and regulation were associated with a significantly reduced prevalence of preeclampsia compared with preprandial blood glucose monitoring and regulation (3% vs 21%; $P < 0.048$). Furthermore, in a prospective, randomized study of combination treatment with short-acting (regular) plus intermediate-acting (NPH) human insulin in 66 patients with gestational DM in the United States, de Veciana et al[7]

found that PPBG monitoring and regulation were associated with improved outcomes in pregnancy (mean [SD] birth weight, 3469 [668] vs 3848 [434] g).

Sulfonylureas (SUs) are a well-established class of drugs used for the management of type 2 DM. They are also the most commonly used first-line oral antidiabetic agents.[8] One second-generation SU, gliclazide, is a well-established oral hypoglycemic agent used in the management of type 2 DM. Gliclazide, like all SUs, promotes insulin secretion by closing adenosine triphosphate–sensitive potassium channels in the pancreatic β-cell membrane, resulting in opening of voltage-dependent calcium channels and subsequently increasing intracellular Ca^{2+}, which induces phosphorylation of proteins, which in turn stimulate insulin release.[9,10] The dose-response relationship of gliclazide has not been firmly established. Nonetheless, gliclazide is extensively used in South Africa.

The epidemiologic evidence supporting PPBG monitoring and regulation and the dose-response relationships of SUs[11]—gliclazide[12] in particular—motivated the present study. The aims of this study were to determine the effects of increasing doses of gliclazide on postprandial glucose excursions after a standardized breakfast and lunch, and to clarify the relationship between gliclazide dose and glucose response.

PATIENTS AND METHODS

This prospective, open-label, case-controlled, dose-escalation study was conducted at the Addington Hospital Diabetes Clinic, a tertiary referral hospital in eThekwini/Durban, KwaZulu-Natal, South Africa. The study protocol was approved by the ethics committee at the University of Durban-Westville, South Africa. Permission to conduct the study at Addington Hospital was obtained from the KwaZulu-Natal Department of Health and the manager of Addington Hospital. The study was conducted in accordance with the Declaration of Helsinki and its amendments[13] and the Patients' Rights Charter.[14] All patients provided written informed consent to participate.

Inclusion and Exclusion Criteria

Male and female patients were identified using the medical records of the clinic; those meeting the inclusion criteria and consenting to participate in the study were enrolled. Patients were not compensated for their participation. Inclusion criteria were as follows: age, ≥18 years; type 2 DM (duration, ≥6 months); current treatment with an oral hypoglycemic agent; capillary FBG level, 8 to 10 mmol/L (144–180 mg/dL); HbA_{1c} concentration, 8% to 10%; and postprandial hyperglycemia ($PPBG_{2\,h}$, ≥11.1 mmol/L [≥200 mg/dL]).

Exclusion criteria were as follows: significant renal impairment (serum creatine level, >1.8 mg/dL); impaired liver function (alanine aminotransferase, aspartate aminotransferase, total bilirubin, or alkaline phosphatase >2.5-fold the upper limit of normal); poor compliance, as assessed using a pill count at

each study visit; poorly controlled DM; current or history of alcohol or other drug abuse; hematologic disorder (white blood cell count, $<2.0 \times 10^9$ cells/L; platelet count, $<100 \times 10^9$ cells/L); congestive heart failure; and porphyria. Women who were pregnant or breastfeeding also were excluded.

Study Drug Administration and Efficacy Assessments

The primary efficacy end points were changes in $PPBG_{2\ h}$ and 6-hour PPBG ($PPBG_{6\ h}$) with dose increase. Secondary efficacy end points were changes in FBG level, area under the blood glucose–time curve from time 0 to 6 hours after breakfast (AUC_{0-6}), and MBG level.

The study included a screening visit (week –1), a 1-week washout period, and 4 additional clinic visits (weeks 0 [baseline], 2, 4, and 6). Hematology (full blood cell count) and biochemistry (liver and kidney function tests; serum lipid levels; HbA_{1c}; serum levels of fructosamine, creatinine, electrolytes, and CO_2; urea; and FBG) were performed in all patients. Anthropomorphic measurements (height, weight, and waist and hip circumferences) also were determined. Full body examinations, including vital sign measurements, were performed by the resident medical practitioner (M.L.). Also at the screening visit, eligible patients were asked to discontinue all treatment with oral hypoglycemic agents for 1 week (washout period) and throughout the study. Treatment with other concomitant medications was continued and itemized throughout the study. Patients received instructions from a nurse on using a home glucose monitor (Glucostix, Ames Division, Miles Laboratories, Elkhart, Indiana) and were asked to record their FBG levels each day on waking in a patient diary during the washout period. Patients received counseling on appropriate diet from the resident dietician, and were asked to record and report any major changes in dietary or exercise habits throughout the study.

One week after screening (week 0; baseline), patients returned to the clinic after an overnight fast, and a blood sample was drawn to determine fasting levels of serum fructosamine, plasma insulin, and blood glucose. A standardized breakfast was then administered, followed by a standardized lunch 4 hours later. The researcher (P.N.) observed the complete consumption of the meals, which occurred within ~10 minutes. To determine AUC_{0-6}, blood glucose levels were measured at 30-minute intervals for 6 hours after breakfast; these measurements included $PPBG_{2\ h}$ and $PPBG_{6\ h}$. Plasma insulin was measured again 30 minutes after breakfast. At the end of the baseline visit, patients were supplied with gliclazide 80-mg tablets, to be self-administered at 40 mg (1/2 tablet) QD in the morning with a meal and ~250 mL water for 2 weeks, commencing the following morning.

At week 2, patients returned to the clinic after an overnight fast and received gliclazide 40 mg 15 minutes before a standardized breakfast was administered. A standardized lunch was administered 4 hours after breakfast. Blood glucose was measured at 30-minute intervals for 6 hours after breakfast; these measurements included $PPBG_{2\ h}$ and $PPBG_{6\ h}$. Fructosamine and insulin were measured as during the baseline visit. At the end of the week-2 visit, patients were asked

to begin self-administering a dose of 80 mg QD for 2 weeks, beginning on the following morning.

Measurements at week 4 were performed as during week 2; the gliclazide dose was increased to 160 mg QD. Measurements at week 6 (study end) were performed as during screening (hematology, biochemistry, anthropomorphic measurements, and full body examination) and fructosamine, insulin, and glucose were measured as at weeks 2 and 4. On completion of the study, all patients were reintegrated into the diabetes clinic (ie, resumed their usual oral hypoglycemic agent treatment). **Figure 1** and **Table I** provide a synopsis of the study procedures and the assessments conducted at each visit, respectively.

Based on recommendations from the American Diabetes Association (ADA),[15] *acceptable clinical control of postprandial hyperglycemia* was defined as a $PPBG_{2\,h}$ level 8 to 10 mmol/L (144–180 mg/dL). The proportion of patients who

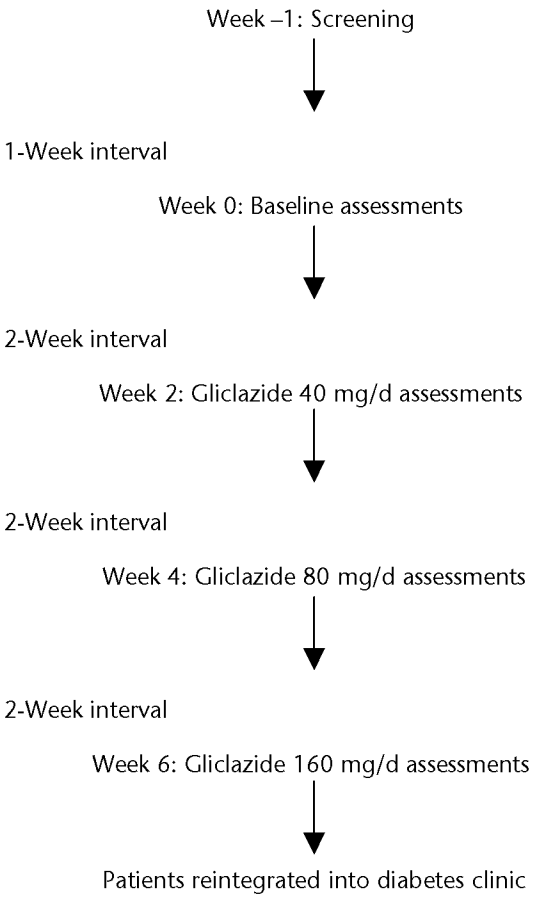

Figure 1. Study procedure.

Table I. Outline of study assessments.

Assessment	Week –1 (Screening)	Week 0 (Baseline)	Week 2 (Gliclazide 40 mg/d)	Week 4 (Gliclazide 80 mg/d)	Week 6 (Gliclazide 160 mg/d)
Hematology	√	–	–	–	√
Liver function tests	√	–	–	–	√
Kidney function tests	√	–	–	–	√
Serum lipid levels	√	–	–	–	√
HbA_{1c}	√	–	–	–	√
Fasting serum fructosamine	√	√	√	√	√
Serum creatinine	√	–	–	–	√
Urea	√	–	–	–	√
Electrolytes and CO_2	√	–	–	–	√
FBG	√	√	–	√	√
Anthropometric measures	√	–	–	–	√
Full body examination	√	–	–	–	√
FPI	–	√	√	√	√
Blood glucose q 30 min for 6 h	–	√	√	√	√
Blood insulin 30 min after standardized breakfast	–	√	√	√	√
PPBG	–	√	√	√	√
Adverse effects	–	–	√	√	√

√ = Assessment performed; – = assessment not performed; HbA_{1c} = glycosylated hemoglobin; FBG = fasting blood glucose; FPI = fasting plasma insulin; PPBG = postprandial blood glucose.

achieved acceptable control of postprandial hyperglycemia was determined at each study visit.

Patients were withdrawn from the study if they withdrew their consent, experienced signs and/or symptoms of hypoglycemia, and/or had a blood glucose level <3.2 mmol/L (<57.6 mg/dL) at any stage of the study.

Laboratory Analysis

All liver and kidney function tests and glycemic measurements were performed at the laboratory at Addington Hospital. Blood sampling was carried out by the resident physician as per hospital protocol. Approximately 10 mL of blood was drawn for each sample. At the clinic, blood glucose was measured using a glucose meter (Accucheck Active, Roche Diagnostics, Mannheim, Germany). The finger-prick method provided rapid (~5 seconds) results and allowed for early detection of extremes in blood glucose levels and institution of remedial measures. The accuracy of the results of the finger-prick test were confirmed using standard laboratory analysis of $PPBG_{2\ h}$. Insulin levels were determined using an insulin electrochemiluminescence immunoassay kit (Elecsys

Systems D-68298, Roche Diagnostics). Analysis of HbA_{1c} was carried out using the Cobas Integra method (Roche Diagnostics, Inc., Somerville, New Jersey).

Anthropometric Measures

Height was measured using a stadiometer, and weight was obtained using a standard electronic digital scale. Waist circumference was obtained at the level of the umbilicus, and hip circumference was measured at the maximum circumference around the hips. This methodology was similar to that adopted by Tulloch-Reid et al.[16]

Glucose Profiles

MBG was determined as follows:

MBG = [(Sum of glucose levels during the 6-hour assessment period for patient 1/n) + (Sum of glucose levels for patient 2/n) ... /N]

where n = the number of glucose measurements during the 6-hour study period, and N = total number of patients.

Surrogate Measures of Insulin Resistance and Insulin Secretion

The homeostatic model assessment (HOMA)-2 calculator software (University of Oxford, Oxford, United Kingdom) was used to determine HOMA-IR, which is a surrogate marker of insulin resistance (IR) and was used to describe the IR status of the study cohort. Patients with HOMA-IR values >1.57 were classified as insulin resistant. Acute insulin release (AIR) was calculated as the difference in insulin levels at 30 and 0 minutes, and served as a surrogate marker of first-phase insulin secretion. *Response* was defined as HOMA-IR ≤1 and any increase in AIR. The rate of response was determined at study end.

Tolerability Assessment

Adverse-effect monitoring included direct reporting of untoward effects to the resident medical practitioner (M.L.), clinical examination, monitoring of home blood glucose records, hematology, and liver and kidney function tests.

Compliance Assessment

Compliance was assessed using pill counts, examination of diary entries, and patient interview. Compliance was enforced using telephone calls to the patients each day.

Statistical Analysis

A sample size of 11 patients was required to detect a difference of 2 mmol/L (36 mg/dL) between any two levels of glucose, with a probability of 0.05 and 80% power, assuming a constant SD of 3.22 mmol/L (58 mg/dL) at each dose interval. Buoen et al[17] assessed cohort size in Phase I dose-escalation trials and concluded that a sample size of ≥10 patients was sufficient.

Continuous variables are expressed as mean (SD) unless otherwise stated. The paired samples *t* test was used to determine differences between continuous variables at 95% CI. Statistical significance was assumed for *P* values <0.05. Data collection and statistical analysis were performed using SPSS version 11.5 (SPSS Inc., Chicago, Illinois).

RESULTS

Study Population

Of the 33 patients who were screened, 14 satisfied the inclusion criteria and were enrolled in the study. Thirteen patients completed the study (7 women, 6 men; mean [SD] age, 52.0 [11.1] years). One patient was withdrawn because of poor compliance. Seven patients not currently receiving antihypertensive treatment did not reach the ADA[15] optimal blood pressure of <130/80 mm Hg.

In 11 (84.6%) patients, the duration of DM was between 0 and 5 years. All 13 patients had hyperlipidemia (low-density lipoprotein cholesterol level, >3.9 mmol/L; total cholesterol level, >5.9 mmol/L; triglyceride level, >1.84 mmol/L). Eleven patients were categorized as obese based on World Health Organization criteria (body mass index, ≥30 kg/m^2).[18] On entry, 9 (69.2%) patients had IR. However, 12 patients had elevated globulin levels (mean [SD] in patients with elevated globulin levels, 36 [4] g/L [normal range, 20–32 g/L]). The hematologic parameters were within the normal ranges at baseline and at the completion of the study in all 13 patients. The demographic characteristics and baseline biochemistry and hematology of the study cohort on entry are presented in **Table II** and **Table III**, respectively.

Efficacy

Table IV shows the glycemic measurements found in the study population. Mean levels of $PPBG_{2\ h}$ and $PPBG_{6\ h}$ at each dose of gliclazide are depicted in **Figures 2** and **3**, respectively, and **Table IV**. The change from baseline in mean $PPBG_{2\ h}$ was not statistically significant with gliclazide 40 mg/d. Mean (SD) $PPBG_{2\ h}$ was significantly reduced from baseline with doses of 80 and 160 mg/d (from 12.5 [4.6] to 10.1 [4.4] and 10.5 [4.1] mmol/L, respectively [from 225.2 [82.9] to 181.9 [79.3] and 189.2 [73.9] mg/dL, respectively]; $P = 0.005$ and $P = 0.011$, respectively). Mean $PPBG_{2\ h}$ did not change significantly with dose escalation from 80 to 160 mg/d (**Figure 2** and **Table IV**).

Mean (SD) $PPBG_{6\ h}$ was significantly reduced from baseline with all 3 doses of gliclazide (40, 80, and 160 mg/d) (from 13.9 [4.3] to 10.1 [3.8], 9.5 [4.2], and 10.3 [4.1] mmol/L, respectively [from 250.4 [77.5] to 181.9 [68.5], 171.1 [75.7], and 185.6 [73.9] mg/dL, respectively]; $P = 0.001$, $P = 0.001$, and $P = 0.005$, respectively). The difference in mean $PPBG_{6\ h}$ was not significantly different between the 40- and 80-mg/d doses. However, there was a statistically significant decrease in mean $PPBG_{6\ h}$ when the gliclazide dose was increased from 80 to 160 mg/d ($P = 0.018$) (**Figure 3** and **Table IV**).

Table II. Demographic characteristics of study patients (N = 13).

Characteristic	Value
Age, y	
Mean (SD)	52.0 (11.1)
Range	37–77
95% CI	46–58
Sex, no. (%)	
Female	7 (53.8)
Male	6 (46.2)
Race, no. (%)*	
Asian	9 (69.2)
Black	2 (15.4)
White	1 (7.7)
Mixed	1 (7.7)
Disease duration, no. (%)	
0–<5 y	11 (84.6)
5–<10 y	1 (7.7)
≥10	1 (7.7)
Weight, kg	
Mean (SD)	82.4 (18.1)
Range	48.5–116.0
95% CI	72.6–92.2
Height, cm	
Mean (SD)	167 (10)
Range	155–182
95% CI	162–172
BMI (kg/m^2)	
Mean (SD)	29.48 (5.87)
Range	18.70–41.10
95% CI	26.29–32.67
Waist/hip ratio (all patients)	
Mean (SD)	1.0 (0.1)
Range	0.9–1.2
95% CI	9.9–1.1
Waist circumference, cm, mean (SD)	
Women	106 (17)
Men	96 (12)
Received OHAs before washout, no. (%)	
Metformin	5 (38.5)
Glibenclamide	8 (61.5)

BMI = body mass index; OHA = oral hypoglycemic agent.
*Percentages do not total 100% due to rounding.

Table III. Baseline biochemistry and hematology in the study patients (N = 13).

Parameter	Normal Value	Mean (SD)	Value	95% CI
Hematology				
Red blood cell count, × 10^{12} cells/L	4.50–6.50	4.84 (0.52)	4.12–6.05	4.56–5.12
Hemoglobin, g/dL	13.0–17.0	13.5 (1.8)	9.2–15.8	12.5–14.5
Hematocrit, %	42.00–52.00	41.00 (4.11)	31.91–46.40	38.77–43.23
Mean corpuscular volume, fL[a]	78.0–96.0	83.3 (6.0)	68.1–89.6	80.0–86.6
Mean corpuscular hemoglobin, pg	26.0–32.0	27.6 (3.2)	19.7–31.0	25.9–29.3
Mean corpuscular hemoglobin concentration, g/dL	32.0–36.0	33.3 (1.9)	28.9–35.8	32.3–34.3
Red cell distribution width, %	12.5–14.5	13.7 (1.5)	12.2 (17.9)	12.9–14.5
Platelets, × 10^9 cells/L	150–400	278 (64)	192 (427)	275–282
Mean platelet volume, fL[a]	7.4–12.4	9.2 (0.9)	7.8 (10.9)	8.7–9.7
White blood cell count, × 10^9 cells/L	4.0–11.0	8.0 (2.2)	5.6–12.8	6.8–9.2
Electrolytes and carbon dioxide, mmol/L*				
Sodium	131–147	137 (2)	133–139	136–138
Potassium	3.9–5.3	4.6 (0.3)	4.2–5.2	4.4–4.8
Chloride	96–108	103 (3)	99–109	101–105
CO_2	24–32	27 (2)	22–30	26–28
Biochemistry				
Glycemic parameters				
FBG, mmol/L[b]	8.7–9.6	9.1 (0.8)	0.8–7.6	7.6–10.0
HbA_{1c}, %	4.8–6.0	8.7 (1.8)	6.0–12.0	7.7–9.6
Fructosamine, µmol/L	50–285	349 (78)	249–484	307–391

(continued)

Table III. (Continued)

Parameter	Normal Value	Mean (SD)	Value	95% CI
Serum lipids, mmol/L				
TC[c]	3.6–5.1	6.4 (1.4)	3.4–9.0	5.6–7.1
LDL-C[c]	≤3.90	3.97 (1.07)	2.03–5.27	3.39–4.55
HDL-C[c]	≥1.42 (men); ≥1.68 (women)	1.50 (0.16)	0.79–6.90	0.52–2.49
TG[d]	0.39–1.84	3.00 (2.46)	0.81–8.89	166.00–4.34
LFTs				
ALT, U/L	10–60	29 (13)	13–52	22–36
ALP	59–115	85 (26)	71–99	42–121
Total bilirubin, µmol/L[e]	3–17	12 (4)	4–19	10–14
Total protein, g/L[f]	60–80	76 (4)	70–84	74–78
Albumin, g/L[f]	32–50	40 (3)	34–47	38–42
Globulin, g/L[g]	20–32	36 (4)	31–45	34–38
GGT, U/L	7–64	39 (23)	9–78	26–52
Renal function				
Urea, mmol/L[h]	2.7–7.4	4.4 (1.2)	2.5–6.3	3.7–5.1
Serum creatinine, µmol/L[i]	64–112	69 (14)	51–96	61–77

FBG= fasting blood glucose; HbA_{1c} = glycosylated hemoglobin; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; LFTs = liver function tests; ALT = alanine aminotransferase; ALP = alkaline phosphatase; GGT = γ-glutamyltransferase.
To convert to convention units, divide by the following[19]: [a]0.06206; [b]0.05551; [c]0.02586; [d]0.01129; [e]17.1; [f]10; [g]0.01; [h]0.357; [i]88.4.
*mmol/L = mEq/L.

Table IV. Glycemic measures at baseline (week 0) and throughout the treatment period in patients receiving gliclazide for postprandial hyperglycemia (N = 13).[a] Values are mean (SD).

Parameter	Week 0 (Baseline)	Week 2 (40 mg/d)	Week 4 (80 mg/d)	Week 6 (160 mg/d)
$PPBG_{2\,h}$, mmol/L	12.5 (4.6)	12.5 (4.2)	10.1 (4.4)[b]	10.5 (4.1)[c]
$PPBG_{6\,h}$, mmol/L	13.9 (4.3)	10.1 (3.8)[d]	9.5 (4.2)[d]	10.3 (4.1)[b,e]
FBG, mmol/L	11.6 (3.2)	11.8 (3.7)	9.6 (2.9)[f]	9.8 (3.5)[g]
AUC_{0-6}, mmol · h/L	76.3 (22.4)	67.7 (21.4)[h]	59.9 (20.8)[i,j]	61.0 (20.9)[i]
MBG, mmol/L	12.7 (4.2)	11.3 (4.2)[k]	10.0 (3.9)[j,k]	10.2 (3.9)[k]

$PPBG_{2\,h}$ = postprandial (2 h) blood glucose; $PPBG_{6\,h}$ = postprandial (6 h) blood glucose; FBG = fasting plasma glucose; AUC_{0-6} = area under the blood glucose–time curve from 0 to 6 hours after administration of standardized breakfast; MBG = mean blood glucose.
[a]To convert to conventional units,[19] divide by 0.05551; [b]$P = 0.005$ versus baseline; [c]$P = 0.011$ versus baseline; [d]$P = 0.001$ versus baseline; [e]$P = 0.018$ versus 80 mg; [f]$P = 0.028$ versus baseline; [g]$P = 0.035$ versus baseline; [h]$P = 0.029$ versus baseline; [i]$P = 0.003$ versus baseline; [j]$P < 0.001$ versus 40 mg; [k]$P < 0.001$ versus baseline.

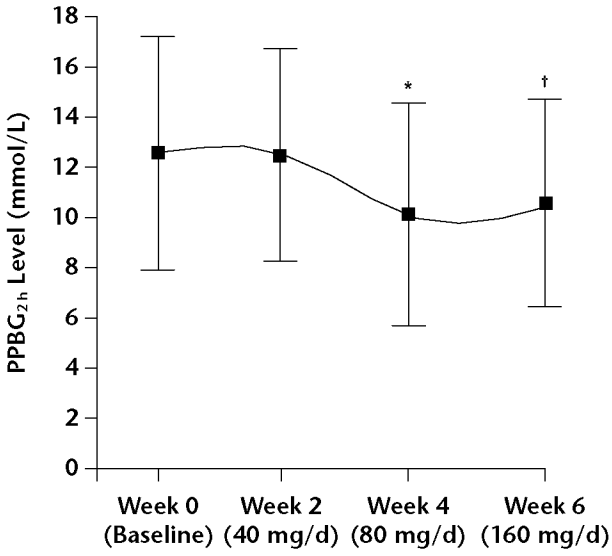

Figure 2. Mean (SD) 2-hour postprandial blood glucose ($PPBG_{2\,h}$) levels at baseline (week 0) and throughout the treatment period in patients receiving gliclazide for postprandial hyperglycemia (N = 13). *$P = 0.005$ versus baseline; †$P = 0.011$ versus baseline.

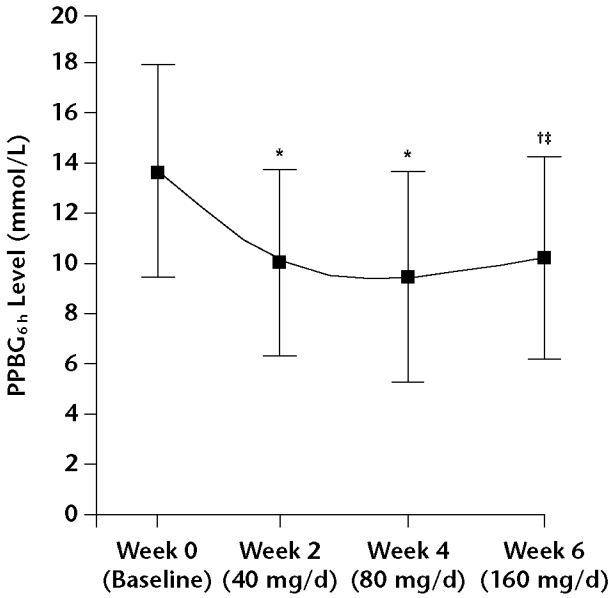

Figure 3. Mean (SD) 6-hour postprandial blood glucose ($PPBG_{6\,h}$) levels at baseline (week 0) and throughout the treatment period in patients receiving gliclazide for postprandial hyperglycemia (N = 13). *P = 0.001 versus baseline; †P = 0.005 versus baseline; ‡P = 0.018 versus 80 mg.

Nine (69.2%) patients achieved acceptable clinical control of postprandial hyperglycemia at the 80-mg/d dose. Dose escalation from 80 to 160 mg/d did not increase the number of patients achieving target PPBG levels.

Figure 4 and **Table IV** show the changes in mean FBG with dose. Mean FBG was not significantly reduced from baseline with the 40-mg/d dose of gliclazide. However, the mean FBG concentration was significantly reduced from baseline with the 80- and 160-mg/d doses of gliclazide (from 11.6 [3.2] to 9.6 [2.9] and 9.8 [3.5] mmol/L, respectively [from 209.0 [57.6] to 172.9 [52.2] and 176.5 [63.1] mg/dL, respectively]; P = 0.028 and P = 0.035, respectively). There was no significant difference in mean FBG between the 80- and 160-mg/d doses of gliclazide. **Figure 4** shows the "plateau effect" on FBG as the dose of gliclazide reaches 160 mg/d.

Figure 5 depicts the blood glucose–time profiles throughout the study. The 80- and 160-mg/d doses of gliclazide appeared to be associated with similar glucose profiles, suggesting a minimal difference between these 2 doses when the blood glucose–time profiles are used as the pharmacodynamic marker (plateau effect).

The AUC_{0-6} values at each dose are shown in **Figure 6**. Mean (SD) AUC_{0-6} values were significantly reduced from baseline at the 40-, 80-, and 160-mg/d doses of gliclazide (from 76.3 [22.4] to 67.7 [21.4], 59.9 [20.8], and 61.0 [20.9] mmol · h/L, respectively [from 1374.5 (403.5) to 1219.6 (385.5), 1079.1 (374.7), and 1098.9

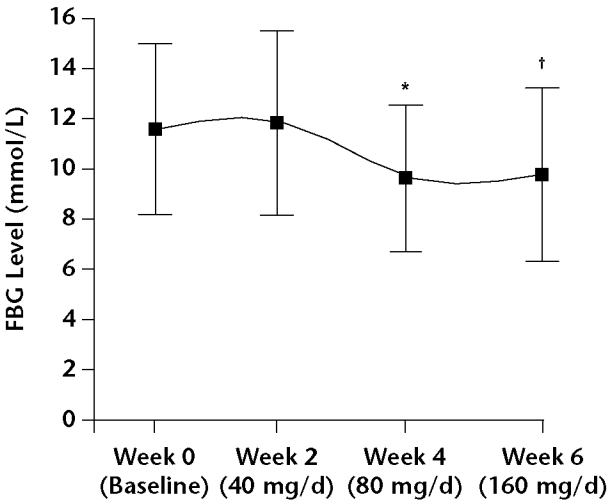

Figure 4. Mean (SD) fasting blood glucose (FBG) levels at baseline (week 0) and throughout the treatment period in patients receiving gliclazide for postprandial hyperglycemia (N = 13). *P = 0.028 versus baseline; †P = 0.035 versus baseline.

(376.5) mg · h /dL, respectively]; $P = 0.029$, $P = 0.003$, and $P = 0.003$, respectively). There was a progressive reduction in the mean AUC_{0-6} value as the dose of gliclazide was increased from 40 to 80 mg/d ($P < 0.001$). However, the difference between the 80- and 160-mg/d doses was nonsignificant.

Mean (SD) MBG concentrations were significantly reduced from baseline with gliclazide 40, 80, and 160 mg/d (from 12.7 [4.2] to 11.3 [4.2], 10.0 [3.9], and 10.2 [3.9] mmol/L, respectively [from 228.8 (75.7) to 203.6 (75.7), 180.1 (70.3), and 183.8 (70.3) mg/dL, respectively]; all, $P < 0.001$) (**Figure 7** and **Table IV**). The reduction in mean MBG concentration was statistically significant when gliclazide was increased from 40 to 80 mg/d ($P < 0.001$). However, the difference in mean MBG concentrations between the doses of 80 and 160 mg/d was nonsignificant.

The AUC_{0-6} and MBG values were consistent with those of the full glucose-time profiles. No significant differences in HbA_{1c} were found (**Figure 8**).

Surrogate Measures of Insulin Resistance and Insulin Secretion

On entry, 2 of 11 (18.1%) patients with available data had insulin sensitivity as defined on HOMA-IR (**Table IV**). The number of patients with insulin sensitivity was not altered with gliclazide administration; 2 (18.1%) patients were insulin sensitive on completion of the study.

The numbers of patients with a significant increase from baseline in AIR seemed similar with gliclazide 40 and 80 mg/d (7 and 8 patients, respectively) (**Table V**). However, dose escalation from 80 to 160 mg/d resulted in 4 (30.8%) patients showing an apparent decrease in AIR.

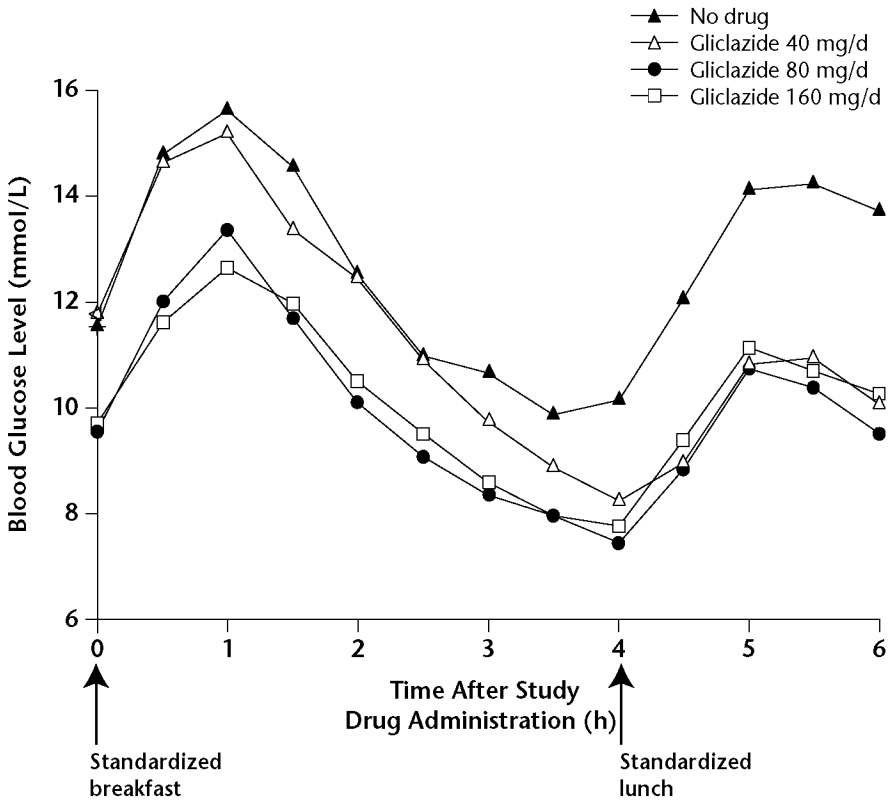

Figure 5. Mean blood glucose excursions versus time profiles at baseline (week 0) and throughout the treatment period in patients receiving gliclazide for postprandial hyperglycemia (N = 13).

Tolerability

None of the patients reported or were found to have any adverse effects.

DISCUSSION

The high prevalences of IR, obesity, hyperlipidemia, and hyperglycemia at baseline in this study suggest that the cohort had features characteristic of the metabolic syndrome.

The maximum percentage reductions in $PPBG_{2\,h}$ and $PPBG_{6\,h}$—19% and 32%, respectively—were similar to those reported in previous studies (range, 18%–25%).[20–24] The minimum dose at which the greatest number of patients (9 [69.2%]) achieved acceptable clinical control of postprandial hyperglycemia was 80 mg/d, emphasizing that patients should undergo a trial of SUs (eg, glic-

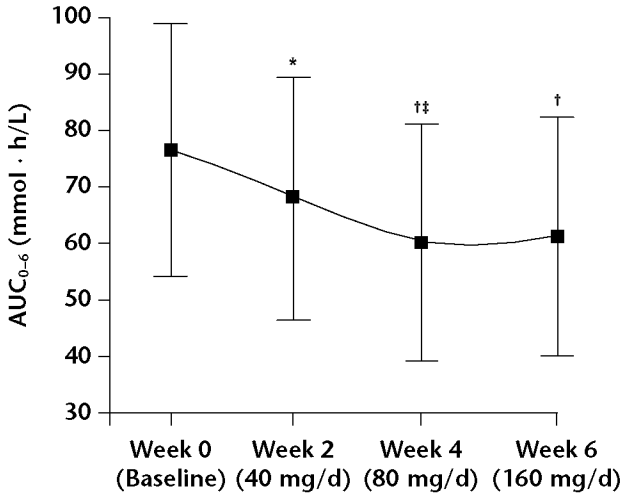

Figure 6. Mean (SD) area under the blood glucose–time curve from time 0 to 6 hours after study drug administration (AUC_{0-6}) at baseline (week 0) and throughout the treatment period in patients receiving gliclazide for postprandial hyperglycemia (N = 13). *$P = 0.029$ versus baseline; †$P = 0.003$ versus baseline; ‡$P < 0.001$ versus 40 mg.

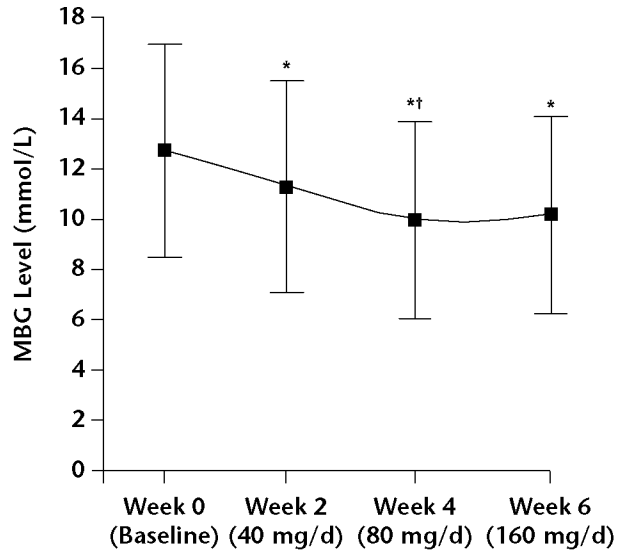

Figure 7. Mean (SD) mean blood glucose (MBG) levels at baseline (week 0) and throughout the treatment period in patients receiving gliclazide for postprandial hyperglycemia (N = 13). *$P = 0.001$ versus baseline; †$P < 0.001$ versus 40 mg.

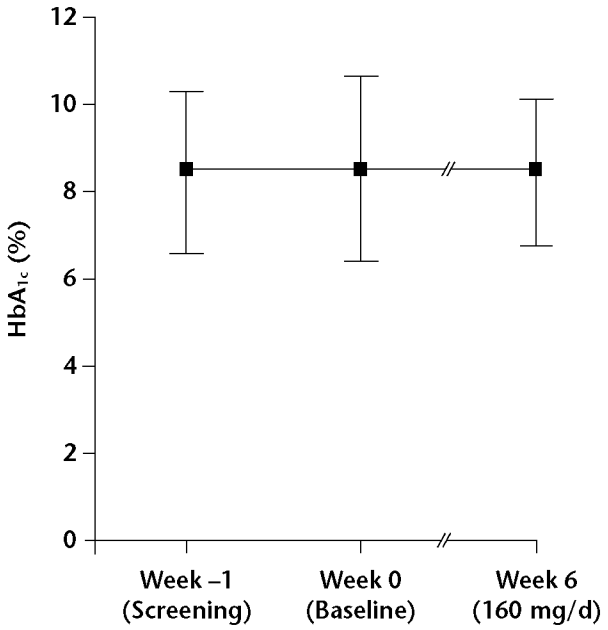

Figure 8. Mean (SD) glycosylated hemoglobin (HbA_{1c}) concentrations before and after treatment in patients receiving gliclazide for postprandial hyperglycemia (N = 13).

lazide) before newer agents specifically targeting postprandial hyperglycemia (meglitinides, α-glucosidase inhibitors, rapid-acting insulin analogs) are employed. The fact that the mean $PPBG_{2\,h}$ value did not change significantly with dose escalation from 80 to 160 mg/d suggests that gliclazide 160 mg does not offer any additional benefit in reducing $PPBG_{2\,h}$ compared with 80 mg/d. Furthermore, the significant increase in mean $PPBG_{6\,h}$ from 80 to 160 mg/d (P = 0.018) suggests a deterioration of glycemic control.

Mean FBG was reduced from baseline by 17% and 16% with gliclazide 80 and 160 mg/d, respectively. These reductions appear similar to those reported by Brogard et al,[25] Guillausseau,[20] Sinay et al,[23] and Wing et al[26] (21.7%, 26.7%, 23.8%, and 28.6%, respectively).

FBG is dependent on endogenous glucose production, which, in turn, is dependent on IR and basal insulin secretion.[27] First-phase insulin secretion has been associated with suppression of endogenous glucose production after ingestion of a meal.[28] The loss of first-phase insulin secretion is an important defect in type 2 DM and results in postprandial hyperglycemia. In the present study, AIR served as a surrogate marker of first-phase insulin secretion. Gliclazide 160 mg/d seemed to be associated with impaired AIR, suggesting that it reduced first-phase insulin release. The finding that gliclazide did not improve the prevalence of IR, but improved insulin secretion, in this study population

Table V. Response* at baseline (week 0) and throughout the treatment period in patients receiving gliclazide for postprandial hyperglycemia (N = 13).

Parameter	Week 0 (Baseline)	Week 2 (40 mg/d)	Week 4 (80 mg/d)	Week 6 (160 mg/d)
No. (%) of patients with IR defined as increased AIR	–	7/10 (70.0)	8/10 (80.0)	4/10 (40.0)
No. (%) of patients with IR as determined using HOMA-IR	2/11 (18.2)	0/11 (0)	1/13 (7.7)	2/13 (15.4)

IR = insulin resistance; AIR = acute insulin release; HOMA-IR = homeostatic model assessment–insulin resistance.
**Response* was defined as follows: HOMA-IR ≤1 and any AIR increase compared with baseline.

suggests that gliclazide has a limited effect on insulin sensitivity and that the effect of gliclazide on FBG might be related to basal insulin secretion.

The association of gliclazide with reduced FBG and PPBG levels might result in an option for glycemic control if these effects can be maintained in the long term (~10 years). However, this ideal is unlikely to be achieved because DM is characterized by a progressive decline in pancreatic function,[29,30] which would necessitate combination therapy with insulin sensitizers (eg, biguanides) and/or insulin.[31] The high prevalence of IR in this study cohort (18.1%) further supports the use of combination therapy, particularly with insulin sensitizers. Traditionally, pharmacotherapy for type 2 DM has been aimed at improving glycemic control, with or without correcting IR.[32] In view of the increasing evidence indicating the central role of IR in hypertension, hyperlipidemia, obesity, dysfibrinolysis, and hyperuricemia, the use of SU monotherapy might not be rational because, although it might result in acceptable clinical control of postprandial hyperglycemia initially, it theoretically would not correct the IR that might be present. Because IR is a central feature of the metabolic syndrome, which was prevalent in the present study cohort, the possible failure of gliclazide to effectively improve IR is concerning.

The mean $PPBG_{2\,h}$, FBG, $AUC_{0–6}$, and MBG values were similar at the 80- and 160-mg/d doses, suggesting that dose increments >80 mg/d might not be clinically beneficial (ie, plateau effect). Assessment of the clinical response of the patients found that the proportions of patients who attained acceptable clinical control of postprandial hyperglycemia at 80 and 160 mg/d were similar (69.2% with both doses). However, 1 (7.7%) patient achieved acceptable control at the 160-mg/d dose but not at the 80-mg/d dose, suggesting that a subset of patients might be more responsive to higher doses (eg, 160 mg/d) of gliclazide. This responsiveness of patients to the relatively high dose of gliclazide has been observed with other SUs.[33] Briefly, some subjects responded (ie, achieved FBG 4–6 mmol/L) with glibenclamide 20 mg/d and not 10 mg/d.

The finding of no significant differences in HbA_{1c} was expected due to the short duration of the study (7 weeks). HbA_{1c} typically is used for detecting changes in glycemia over an 8- to 12-week period.

The plateau effect of gliclazide (and other SUs) with dose escalation has been reported previously.[31,33–35] A clinical study of gliclazide in patients with type 2 DM conducted by Shaw et al[12] found that increasing the dose of gliclazide from 80 to 160 mg/d during long-term administration might not increase antihyperglycemic activity. Rambiritch,[33] in a dose-escalation study of glibenclamide 5, 10, 15, and 20 mg/d in 22 patients with type 2 DM in South Africa, found a lack of added glycemic control with doses of glibenclamide >5 to 10 mg/d (mean [SD] FBG levels at doses of 10 and 20 mg/d, 11.5 [3.84] and 11.2 [4.15] mmol/L, respectively; $P = 0.782$). This finding supports the observation by Jonsson et al[34] that maximal therapeutic efficacy of glibenclamide occurred within the dose range of 7.0 mg/d (median HbA_{1c}, 7.2% [range, 6.3%–10.3%]) to 10.5 mg/d (median HbA_{1c}, 8.0% [range, 6.0%–9.9%]) in a prospective study in 50 patients with type 2 DM in Sweden. The results of the present study agree with the growing consensus that maximal reductions in glycemia are found with SU doses approximately half the manufacturers' maximum recommended daily dose.[31,35]

This study found a statistically significant increase in $PPBG_{6\ h}$ ($P = 0.018$), indicating a decrease in glycemic control, when the dose of gliclazide was increased from 80 to 160 mg/d. The maximum manufacturer's recommended dose[10] of 320 mg/d was not used in this study. Therefore, it is speculative as to what effect the higher dose of gliclazide would have had. If the trend toward reduced glycemic control with doses >80 mg/d were to continue, then higher doses would have produced a paradoxical increase in blood glucose levels. However, based on a MEDLINE search for literature concerning gliclazide (key terms: *gliclazide*, *dose escalation*, and *efficacy*; years: 1970–2005), no studies have found a deterioration of glycemic control with high doses of gliclazide. Nonetheless, this phenomenon has been described for other SUs (eg, glipizide[36,37] and glibenclamide[33,38]). Dose escalation from 80 to 160 mg/d was associated with an apparent reduction in AIR, which might explain the apparent deterioration in glycemic control. However, the reason for high-dose SUs impairing glycemic control requires elucidation. It is tempting to speculate that this impairment might be due to the SU-induced hyperinsulinemia, which consequently would increase appetite and food intake, leading to glucotoxicity, although, based on our literature search, no published data are available. In a prospective study of glibenclamide in 15 patients with type 2 DM in South Africa by Jackson and Robertson,[38] this increase in appetite and food intake was described as patients "eating to keep up with their glibenclamide dose."

Because the doses of many pharmacologic agents in diverse drug classes have been altered from those recommended by the manufacturer,[39] we recommend that the efficacy and tolerability of less-than-recommended doses of SUs be reviewed through postmarketing surveillance.[40]

Study Limitations

The generalizability of the findings of the present study is limited because this study was of a short duration (7 weeks) and the sample size was small (n = 13). Gliclazide was not escalated to the maximum manufacturer's recommended dose of 320 mg/d because of the potential danger of hypoglycemia and because this dose is not commonly prescribed in clinical practice in South Africa. Although no adverse effects of gliclazide were found or reported, the small sample size might have limited their detection.

CONCLUSIONS

In this study of gliclazide dose escalation in patients with type 2 DM and postprandial hyperglycemia, gliclazide 80 mg/d effectively reduced postprandial hyperglycemia. Dose escalation from 80 to 160 mg/d was not found to be clinically beneficial with regard to postprandial hyperglycemia. Based on these results, we recommend that gliclazide dose escalation to the maximum dose recommended by the manufacturer be guided by measures of glycemia.

ACKNOWLEDGMENTS

We gratefully acknowledge the financial assistance provided by the University of Durban-Westville, South Africa, and the donation of gliclazide by Sandoz, Johannesburg, South Africa.

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Address correspondence to: Poobalan Naidoo, BPharm, University of KwaZulu-Natal, Faculty of Health Sciences, Westville Campus, Discipline of Pharmacology, Private Bag X54001, Durban 4000, South Africa. E-mail: naidoopo@ukzn.ac.za