Chronic Sulfonylurea Therapy Augments Basal and Meal-Stimulated Insulin Secretion While Attenuating Insulin Responses to Sulfonylurea Per Se

H. DAVID MCINTYRE, MB, BS
ALAN MA, PHD
DOMINIQUE M. BIRD, MD
CAROL A. PATTERSON, BSC
DONALD P. CAMERON, MD

OBJECTIVE — To examine changes in glycemia and insulin secretion in response to SU per se and in response to a standard diet plus OD or TD SU therapy during chronic GP and GB therapy.

RESEARCH DESIGN AND METHODS — Randomized (between agents and in order of dosing regimens), prospective, open, crossover study among 14 NIDDM patients to compare glucose, insulin, and C-peptide responses to a standard diet and to 10 mg of oral GP or GB taken without food *1)* after 2 wk without therapy, *2)* after 4 wk of either GP (n = 7) or GB (n = 7) treatment OD, and *3)* after 4 wk of TD therapy with the same agent. Each patient received the same drug for maintenance therapy and for assessment of the response to the drug alone.

RESULTS — We observed a comparable reduction in overall glycemia with both agents, with more marked postprandial effects for GP. Similar glucose, insulin, and C-peptide profiles for both agents during OD and TD therapy. Augmented insulin secretion in response to meals contrasting with reduced insulinotropic effects of the drugs per se with chronic therapy.

CONCLUSIONS — Therapeutic equivalence of OD and TD dosing with GP and GB during chronic therapy. In view of the improved insulin secretion in response to nutrient stimuli, the attenuation of responses to SU per se during chronic therapy does not imply impairment of β-cell secretory capacity or represent a therapeutic disadvantage.

FROM THE DEPARTMENT OF DIABETES AND ENDOCRINOLOGY, PRINCESS ALEXANDRA HOSPITAL, WOOLLOONGABBA, QUEENSLAND, AUSTRALIA.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO DR. H. DAVID MCINTYRE, MB, BS, DEPARTMENT OF DIABETES AND ENDOCRINOLOGY, PRINCESS ALEXANDRA HOSPITAL, IPSWICH ROAD, WOOLLOONGABBA, QUEENSLAND 4102, AUSTRALIA.

RECEIVED FOR PUBLICATION 23 AUGUST 1991 AND ACCEPTED IN REVISED FORM 18 JUNE 1992.

SU, SULFONYLUREA; GB, GLIBENCLAMIDE; GP, GLIPIZIDE; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; OD, ONCE-DAILY DOSAGE SULFONYLUREA THERAPY; TD, THRICE-DAILY DOSAGE SULFONYLUREA THERAPY; AUC, AREAS UNDER THE CURVE; ANOVA, ANALYSIS OF VARIANCE; CV, COEFFICIENT OF VARIATION; CI, CONFIDENCE INTERVAL; BMI, BODY MASS INDEX; $AUC_{GLUCOSE}$, AREAS UNDER THE CURVE FOR GLUCOSE; $AUC_{INSULIN}$, AREAS UNDER THE CURVE FOR INSULIN; $AUC_{C\text{-}PEPTIDE}$, AREAS UNDER THE CURVE FOR C-PEPTIDE.

Despite their widespread use in the treatment of diabetes for many years, aspects of the mechanisms of SU drugs during chronic therapy remain controversial. This includes the relative importance of their insulinotropic and extrapancreatic effects (1–4), the importance of dose interval and timing of dose administration in relation to meals (5–7), and the importance of insulin release in response to SU per se, as opposed to enhanced insulin release in response to nutrient stimuli (8,9).

Karam et al. (8) described abolition of the insulin response to intravenous tolbutamide with maintenance of responses to glucose and glucagon after treatment with tolazamide. This effect developed rapidly, being evident within 12 h of the initial dose of tolazamide. More recently, absence of acute insulinotropic effect of oral GB during long-term GB therapy has been described (9). This phenomenon has not, to our knowledge, been described with GP therapy. Some authors have considered abolition of the acute insulinotropic effect of SU per se to be a potentially deleterious effect of chronic SU therapy, representing diminished β-cell function, and have speculated that discontinuous drug exposure may be preferable to continuous exposure in allowing β-cell recovery (10).

The aim of this study was to examine changes in glucose, insulin, and C-peptide responses to a standard diet and to a test dose of SU in patients with NIDDM and chronically treated with SU in three circumstances: *1)* after a washout period without SU therapy, *2)* during OD and *3)* during TD treatment with GP and GB. We hypothesized that discontinuous exposure to SU, as expected with OD GP therapy (7,9), might result in retention of the insulinotropic effect of the drug per se during chronic therapy. We also aimed to further investigate the importance of dose interval in determining responses to chronic SU therapy.

Table 1—*Characteristics of patients treated with GP and GB before entry in the study, and doses administered to each group during the study*

	GP GROUP	GB GROUP
AGE (YR)	66 ± 2	60 ± 2
DURATION OF NIDDM (YR)	12.7 ± 1.5	10.9 ± 1.1
BMI (KG/M^2)	24.8 ± 0.8	26.4 ± 0.9
PRETRIAL HbA$_1$ (%)	9.1 ± 0.7	9.8 ± 0.6
TRIAL DOSE (MG/DAY)	11.8 ± 2.6	15 ± 2.6

Values are means ± SE. No significant differences were observed between the two groups in any parameter.

RESEARCH DESIGN AND METHODS

— This study was approved by the institutional ethics committee, and 14 NIDDM patients participated after giving informed consent. Inclusion criteria were: aged 35–75 yr, BMI 20–30 kg/m^2, normal renal and hepatic function, and current treatment with diet and any SU. Patients were excluded if they were receiving insulin or metformin therapy. The study was prospective and open in design, with each patient randomly allocated to treatment with either GP or GB. The characteristics of the two groups are shown in Table 1.

For the purposes of this study and in light of the data available at the time it was undertaken (3,11,12), GP and GB were considered equipotent on a weight basis, and the following doses of other SUs were considered equivalent to 5 mg of GP or GB: tolbutamide, 1000 mg; gliclazide, 80 mg. Because of the need to administer doses that were multiples of 2.5 mg (to allow dosing with whole and half tablets of each drug), the actual doses administered during the treatment phase of the trial were calculated using the total current daily dose equivalents as outlined above. Patients whose pretrial SU dose translated to 5–10 mg GP or GB equivalent/day received 7.5 mg/day (n = 8). Those who received 11–19 mg equivalent/day were given 15 mg/day (n = 1) of their allocated agent, while those who received 20–29 mg/day were given 22.5 mg/day (n = 5).

Patients' current SU therapy was ceased for 2 wk before the baseline study (basal, study A) was performed. After this study, they received their allocated study drug either OD before breakfast (OD, study B) or TD before meals (TD, study C) in randomized order for 4 wk. The second study then was performed, and each patient changed to the alternative dosing regimen for an additional 4 wk before being admitted for the final study.

Patients were admitted to the hospital for each study and received a standard diet containing 1700 kcal/day (49% carbohydrate, 33% fat, 22% protein). Meals were taken as follows: breakfast at 0830 (500 kcal), lunch at 1230 (600 kcal), dinner at 1800 (600 kcal). Patients remained ambulatory but did not exercise during the studies, and took their medication as allocated for that trial period (nil, OD, or TD), 30 min before meals during each study. An intravenous cannula was inserted into a forearm vein under local anesthesia, and 28-point 24-h profiles of glucose, insulin, and C-peptide were performed on day 1. On day 2 of each study, patients received the same breakfast as day 1 without the study drug. At 1200 on day 2, patients received 10 mg of their allocated study drug without further food, and a 6-point glucose, insulin, and C-peptide profile was performed over a 90-min period.

Plasma glucose was measured using a YSI glucose analyser (model 23 AM, Yellow Springs, OH). Plasma insulin and C-peptide concentrations were measured by radioimmunoassay as described previously (13). Samples from each individual were run in a single assay. The intra-assay CVs for both assays were <5%.

AUC for the glucose, insulin, and C-peptide profiles were calculated by the trapezoid rule. Postprandial excursions were calculated as incremental AUC measured from the start of each meal over a 4-h period. Response to SU alone was calculated by subtracting the value of glucose, insulin, and C-peptide immediately before administration of 10 mg GP/GB at 1200 on day 2 from the maximum value measured over the next 90 min.

Statistical analysis

Comparisons between groups at baseline were performed by unpaired Student's t test. Responses to treatment were compared by ANOVA for repeated measures, with significant overall differences further tested by Tukey's protected t tests. All tests were two-tailed, with 5% considered significant. Results are presented as means ± SE for each of the three studies (basal, OD, and TD), except in Table 2, which shows the total and overnight AUCs as mean (95% CI). To validate the crossover design within each treatment arm, the data also have been analyzed separately for a possible sequence effect by comparison of basal, 4-wk, and 8-wk studies. No sequence effect was found.

RESULTS

— No significant differences were observed between the GP and GB groups in terms of age, duration of diabetes, BMI, pretrial HbA$_1$, or mean SU dose during the trial (Table 1). Treatment was well tolerated by all patients, with no adverse effects observed.

Mean 24-h glucose, insulin, and C-peptide profiles from each stage of the study are shown for GP (Fig. 1) and GB (Fig. 2). Error bars have been omitted for reasons of clarity, but the AUCs have been summarized as mean (95% CI) in Table 2. Basal profiles were similar for the GB and GP groups.

Table 2—*Total (24-h) and overnight AUC for glucose, insulin, and C-peptide after 4 wk without SU (basal) and during OD and TD SU therapy*

	BASAL	OD	TD
GP GROUP (N = 7)			
$AUC_{GLUCOSE}$ (MMOL · HR · L^{-1})			
24-H	366 (273–459)	251 (177–324)*	239 (171–308)*
OVERNIGHT	134 (96–172)	98 (66–131)*	90 (58–122)*
$AUC_{INSULIN}$ (MU · HR · L^{-1})			
24-H	582 (293–870)	922 (403–1440)*	860 (279–1441)*
OVERNIGHT	131 (61–202)	155 (92–218)	161 (65–256)
$AUC_{C\text{-}PEPTIDE}$ (NMOL · HR · L^{-1})			
24-H	26.8 (22.5–31.0)	36 (27.2–44.8)*	34.5 (26.4–42.6)*
OVERNIGHT	8 (6.4–9.6)	9.9 (7.2–12.5)†	10.3 (7.3–13.3)*
GB GROUP (N = 7)			
$AUC_{GLUCOSE}$ (MMOL · HR · L^{-1})			
24-H	340 (246–434)	237 (155–319)*	248 (173–322)*
OVERNIGHT	122 (87–158)	85 (48–122)*	84 (55–122)*
$AUC_{INSULIN}$ (MU · HR · L^{-1})			
24-H	806 (497–1115)	1392 (879–1904)*	1136 (732–1540)*
OVERNIGHT	192 (117–266)	315 (189–441)*	281 (170–392)†
$AUC_{C\text{-}PEPTIDE}$ (NMOL · HR · L^{-1})			
24-H	34.1 (19.1–49)	47.5 (33.3–61.8)*	44.2 (30.5–58)*
OVERNIGHT	10.6 (5.6–15.5)	15.6 (10.1–21.1)*	13.7 (8.7–18.7)*

Results are means (95% CI). No significant differences were observed between the two groups in the basal profiles.
* $P < 0.01$ vs. basal AUC.
† $P < 0.05$ vs. basal AUC.

Glucose

Total $AUC_{glucose}$ was reduced by ~30% by both GP and GB therapy ($P < 0.01$, Figs. 1*C*, 2*C*), with no difference noted between OD and TD therapy or between the two agents. Basal glycemia, as assessed by the $AUC_{glucose}$ overnight (2200–0800), showed a similar reduction ($P < 0.01$, Figs. 1*C*, 2*C*).

Meal-stimulated glucose excursions were assessed using changes at breakfast on days 1 and 2 of each study period. Breakfast was chosen over other meals because the preprandial (fasting) glucose was more easily defined, facilitating identification of incremental changes.

Postbreakfast rise in plasma glucose (Fig. 3*C*) was reduced more markedly by GP, with an 80% reduction noted with OD therapy and a 45% reduction with TD therapy ($P < 0.01$ for basal vs. both OD and TD, $P < 0.05$ for OD vs. TD). On day 2 of the treatment studies, when patients received the same breakfast without GP, glucose excursion had returned to baseline levels ($P < 0.01$ compared with day 1 of the same studies, NS compared with basal study). Postbreakfast glucose excursion also decreased with GB therapy (40% with OD, $P < 0.05$; 19% with TD, NS). Day-1 and -2 postbreakfast glucose excursions for each stage of the study were similar during GB therapy.

Insulin

Total $AUC_{insulin}$ (Figs. 1*B*, 2*B*) was increased by both GP (58% with OD, 48% with TD; $P < 0.01$) and GB therapy (76% with OD, 41% with TD; $P < 0.01$). Overnight $AUC_{insulin}$ was increased significantly by GB (64% with OD, $P < 0.01$; 48% with TD, $P < 0.05$), but not by GP.

Postbreakfast insulin excursion (Fig. 3*B*) was more markedly enhanced by GP (189% with OD, $P < 0.05$; 160% with TD, $P < 0.01$). An increase also was seen with GB (80% with OD, 64% with TD), although this did not achieve statistical significance. Day 2 insulin increments were significantly lower than day 1 values with OD GP therapy, ($P < 0.05$), but not with TD therapy.

C-peptide

Changes in C-peptide levels generally paralleled those seen with insulin. Total $AUC_{C\text{-}peptide}$ (Figs. 1*A*, 2*A*) increased both with GP (35% with OD, 30% with TD, $P < 0.01$) and GB (40% with OD, $P < 0.02$; 30% with TD, $P < 0.01$).

Overnight C-peptide levels (Figs. 1*A*, 2*A*) were significantly increased during treatment with both GP (24% with OD, $P < 0.05$; 30% with TD, $P < 0.01$) and GB (46% with OD, 30% with TD, $P < 0.01$).

Postbreakfast C-peptide excursion (Fig. 3*A*) was increased by GP (109% with OD, 84% with TD,

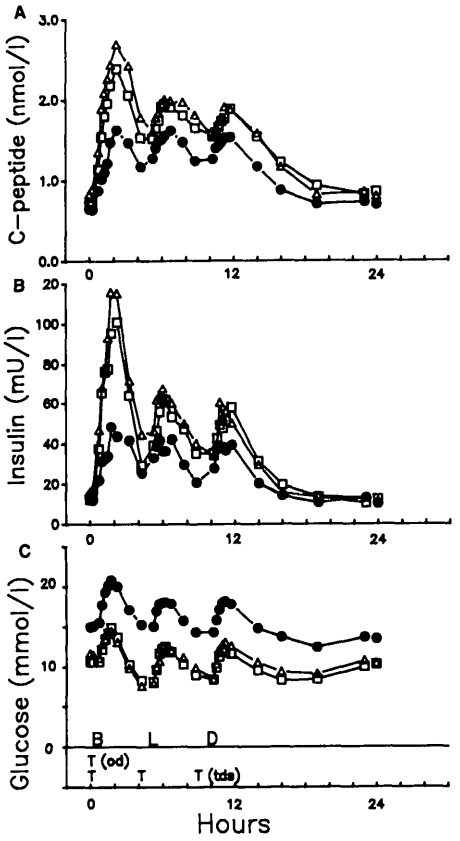

Figure 1—*Twenty-four-hour glucose, insulin, and C-peptide profiles after 2 wk without SU (●——●) and during GP treatment, OD (△——△) and TD (□——□). (T), times of tablet administration, (B), breakfast, (L), lunch, (D), dinner. Error bars have been omitted for reasons of clarity.*

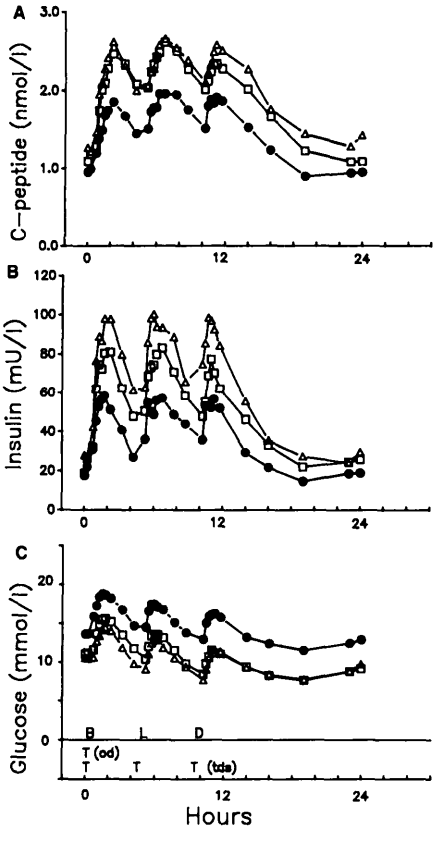

Figure 2—*Twenty-four-hour glucose, insulin, and C-peptide profiles after 2 wk without SU (●——●) and during GB treatment, OD (△——△) and TD (□——□). (T), times of tablet administration, (B), breakfast, (L), lunch, (D), dinner. Error bars have been omitted for reasons of clarity.*

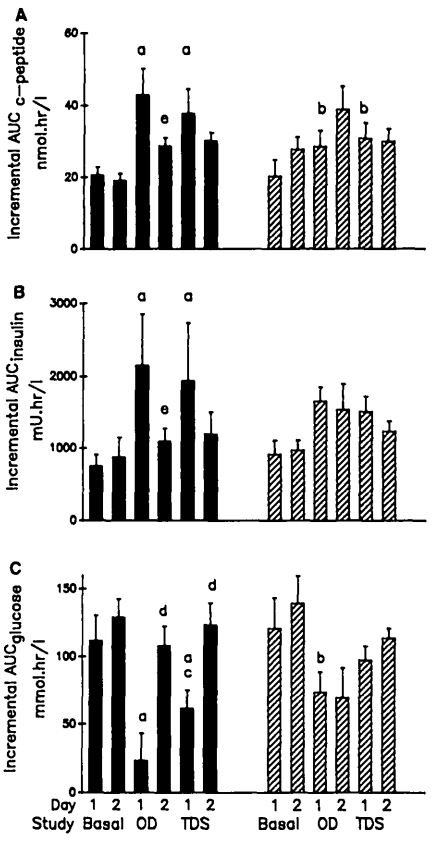

Figure 3—*Mean ± SE incremental AUC after breakfast for glucose, insulin, and C-peptide during treatment with GP (■) and GB (▨), n = 7 for each. (Basal), after 2 wk without SU; (OD), after 4 wk of OD SU; (TDS), after 4 wk of TD SU. (Day 1), SU given before breakfast, for OD and TD; (Day 2), same breakfast without SU. (a), P < 0.01 vs. basal; (b), P < 0.05 vs. basal; (c), P < 0.05 TDS vs. OD; (d), P < 0.01 vs. day 1 of the same study; (e), P < 0.05 vs. day 1 of same study.*

$P < 0.01$) and GB (40% with OD, 52% with TD, $P < 0.05$). C-peptide excursions on day 2 of the studies were significantly reduced compared with day 1 during OD therapy with GP ($P < 0.05$), but not during TD treatment.

No significant differences were observed between OD and TD therapy in terms of their effects on C-peptide profiles.

Response to SU alone

Plasma glucose fell when patients took 10 mg of GP or GB orally without food at 1200 on day 2 of the studies, with similar decrements observed before and after chronic treatment. Plasma glucose concentrations at 1200, immediately before ingestion of the SU tablets were as follows: GB group, basal 16.1 ± 1.9; OD 10.7 ± 1.3; TD 11.8 ± 1.4 mM; GP group: basal 15.6 ± 2.0; OD 11.9 ± 1.7; TD 11.7 ± 1.7 mmol ($P < 0.01$ for basal vs. both OD and TD for both groups, NS between groups).

C-peptide and insulin responses to the first dose of GP alone (study A) were more pronounced than those noted with GB ($P < 0.05$ for both) (Fig. 4). The C-peptide response to GP was reduced by 66% with OD therapy ($P < 0.01$) and 81% with TD therapy ($P < 0.05$). The insulin responses were similarly reduced during chronic therapy (42% with OD, 74% with TD, $P < 0.05$). The insulin and C-peptide responses to GB were small even after the first dose. The C-peptide response fell by 30% with OD (NS) and 65% with TD therapy ($P < 0.05$).

CONCLUSIONS— The major findings of our study were: *1)* comparable reductions in overall glycemia with GP

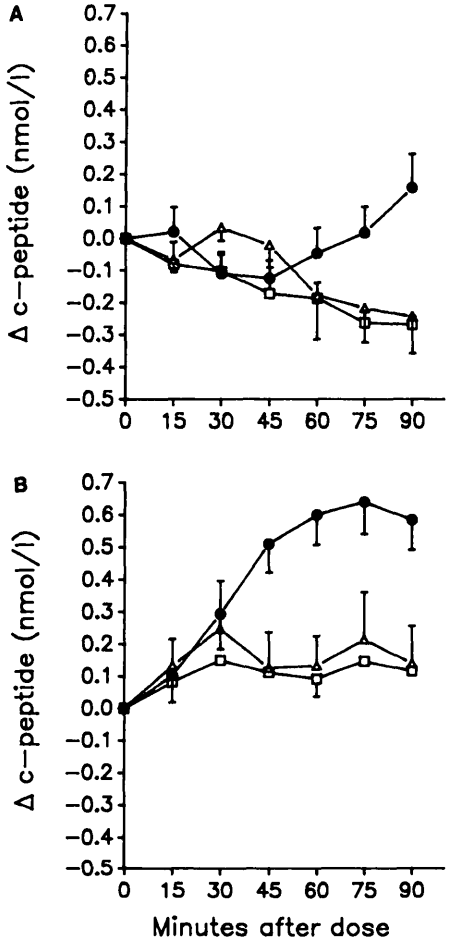

Figure 4—*Mean (SE) incremental C-peptide responses to 10 mg of GB (A) or GP (B), n = 7 for both, after 2 wk without medication (●——●), after 4 wk of OD GP or GB (△——△), and after 4 wk of TD GP or GB (□——□). Each patient received the same drug acutely and for maintenance therapy.*

and GB therapy, with a trend toward greater reduction in postprandial glycemia with GP, 2) overall insulin secretion and glycemic profiles were essentially superimposable for both medications during OD and TD therapy, 3) attenuation of the insulinotropic effect of GP and GB per se was noted during chronic therapy (both OD and TD), contrasting with the augmented insulin secretion in response to meals, and 4) insulin secretion was enhanced during chronic therapy with both agents. The effects of GP were more marked postprandially, whereas those of GB were more marked in the basal state.

In view of the information available at the time these studies were conducted (3,11,12), we considered GP and GB to be approximately equipotent on a weight basis. This assumption since has been questioned by some authors (14,15), who suggested that GB is nearly twice as potent as GP. Within the limits of our study, the assumption of approximate equipotency of GP and GB on a weight basis appears reasonable, although we would stress that the study was not specifically designed to address this issue, and that dose titration was not performed during the study. Thus, the ability of this study to detect a difference between groups was limited. Interestingly, the greater acute first-dose insulinotropic action of GP alone was not reflected by greater overall efficacy in long-term therapy, although it did parallel the more marked postprandial effects of this agent. The apparently greater first-dose insulinotropic effect of GP may have been attributable to its more rapid absorption kinetics (3), and it is possible that more prolonged observations may have shown a greater effect of GB.

In common with previous studies (3), we noted more pronounced effects of GP in reducing glycemia and increasing insulin secretion in the postprandial period, with more marked effects of GB on insulin secretion in the basal state. Unlike some authors (1,16), we noted essentially parallel changes in insulin and C-peptide levels, suggesting true enhancement of insulin secretion rather than a reduction in insulin clearance.

No major differences were noted between glucose, insulin and C-peptide profiles when comparing OD and TD therapy for either agent. The only difference detected was a somewhat lower incremental $AUC_{glucose}$ after breakfast with OD GP therapy, whereas insulin and C-peptide concentrations were similar. Thus, in a pragmatic sense for routine therapy of NIDDM, the difference between these dose intervals does not appear to be important during chronic therapy. This has been noted previously for GP (7). One study noted marginally lower glucose levels when GB (5 mg/day) was taken twice daily before meals rather than as a single daily dose (17). However, the effect was small, being evident only at midnight, and there was no detectable difference in insulin levels. Further, only one day of treatment was given for each dosing regimen, thus limiting the applicability of these findings to chronic therapy.

The effects of GP in improving meal-stimulated insulin secretion waned by day 2 of the studies (when breakfast was taken without the drug). This suggests that 24 h may be approaching the maximum dosing interval for GP, as would be predicted from known pharmacokinetic data (3,7). This effect was not seen with GB, although, as noted, day 1 postprandial effects were less marked with this agent, making detection of differences between days 1 and 2 more difficult. Improved insulin secretion in response to a nutrient stimulus may result from reduction of basal glycemia per se (18). However, if reduced basal glycemia were the only mechanism operating in this case, one would have predicted identical changes in postprandial insulin secretion with GP and GB, given the similar reduction observed in basal glycemia.

Of particular relevance to maintenance therapy of diabetic patients is the contrast between these meal-stimulated effects and the responses to SU alone on day 2 of the studies. The pre-SU glucose levels at the time of administration of SU were significantly lower during chronic therapy. However, based on the study of Vague and Moulin (18) this would not be predicted to have a major effect on the response to SU per se, although the response to other secretagogues such as arginine or isoproterenol could have been impaired (19).

GP showed greater insulinotropic activity in the 90 min after the first dose than GB, as has been observed previously

(20,21). However, during chronic therapy, the overall reductions in total glycemia and increases in insulin secretion achieved by both agents were comparable, suggesting that such acute responses are not a reliable guide to chronic hypoglycemic effects. Further, these acute responses to GP alone were markedly attenuated during chronic therapy, at a time when meal-stimulated and basal insulin secretion were significantly enhanced. This latter observation excludes the possibility of the exhaustion of β-cell secretory reserve during chronic therapy being the cause of reduced response to the tablet per se. Thus, there appears to be a selective impairment of the insulinotropic response to SU per se during SU therapy, demonstrated to date for tolazamide (8), GB (9, this study), and GP. The selective nature of this impairment would argue against the need for intermittent drug exposure in the aim of retaining responses to SU alone. We initially postulated that discontinuous exposure to SU, as predicted from known pharmacokinetic data with GP 7.5 mg OD (3,20), might result in retention of the acute insulinotropic effect of GP alone. However, as seen in Fig. 4, OD therapy and TD therapy were not different in this regard. Even when only those patients taking GP 7.5 mg/day ($n = 5$) were included, retention of acute insulinotropic activity was not observed (data not shown).

Chronic exposure to SU does not appear necessary for attenuation of the insulin response to further SU, as Karam et al. (8) observed such an effect after only 12 h of tolazamide therapy. Indeed, early studies by Raptis et al. (22) and Haupt et al. (23) showed diminished insulinotropic effect of intravenous GB within 3 h of first exposure to the drug.

The mechanism of attenuation of the insulinotropic effects of SU alone with repeated exposure remains undefined. SU drugs are known to bind specifically to high-affinity membrane receptors (24). Such high-affinity binding may block the response to further doses of SU by occupying available receptor sites. In this study, loss of the response to SU was seen even 28 h after the last dose (with OD therapy). Based on known pharmacokinetic data (3,7,20), no detectable SU would be expected to be present in the plasma at this time. This may mean that the SU binding sites are occupied at plasma concentrations lower than those detectable with current methods, or that long-term drug exposure blocks response to further SU by another method, such as downregulation of membrane receptors, as suggested by Karam et al. (8).

Thus, in summary, we have demonstrated enhanced insulin secretion and reduced glycemia, both basally and in response to meals, with GP and GB therapy of up to 8 wk duration. OD and TD therapy with both agents appeared equally effective in augmenting insulin secretion and in improving overall glycemic control. The greater acute first-dose insulinotropic effect of GP alone compared with GB alone was not reflected by a greater improvement in overall glycemia or insulin secretion with chronic therapy. Augmented insulin secretion in response to a mixed-meal stimulus was observed with both GP and GB, contrasting with the attenuated insulin secretion observed in response to SU alone. Ingestion of both food and SU clearly corresponds more closely to the normal everyday situation in patients with NIDDM. Thus, the attenuated response to GP and GB alone seen in this experimental design, although of interest in elucidating the pharmacodynamics of these drugs during chronic therapy, does not, in practical terms, constitute a therapeutic disadvantage during maintenance therapy with either GP or GB.

Acknowledgments— This work was supported by Farmitalia Carlo Erba.

References

1. Hother-Nielsen O, Schmitz O, Andersen PH, Pedersen O, Beck-Nielsen H: In vivo action of glibenclamide in obese subjects with mild type 2 (non—insulin dependent) diabetes. *Diabetes Res* 8:63–70, 1988
2. Yeng C-Y, Hollenbeck CB, Wu M-S, Chen Y-DI, Reaven GM: How does glibenclamide lower plasma glucose concentration in patients with type 2 diabetes? *Diabetic Med* 6:303–308, 1988
3. Groop L, Groop P-H, Stenman S, Saloranta C, Totterman K-J, Fyhrquist F, Melander A: Comparison of pharmacokinetics, metabolic effects and mechanisms of action of glyburide and glipizide during long-term treatment. *Diabetes Care* 10: 671–78, 1987
4. Groop L, Luzi L, Melander A, Groop P-H, Ratheiser K, Simonson DC, DeFronzo RA: Different effects of glyburide and glipizide on insulin secretion and hepatic glucose production in normal and NIDDM subjects. *Diabetes* 36:1320–28, 1987
5. Coppack SW, Lant AF, McIntosh CS, Rodgers AV: Pharmacokinetic and pharmacodynamic studies of glibenclamide in non-insulin dependent diabetes mellitus. *Br J Clin Pharmac* 29:673–84, 1990
6. Batch J, Ma A, Bird D, Noble R, Charles B, Ravenscroft P, Cameron D: The effects of ingestion time of gliclazide in relationship to meals on plasma glucose, insulin and C-peptide levels. *Eur J Clin Pharmacol* 38:465–67, 1990
7. Wahlin-Boll E, Groop L, Karhumaa S, Groop P-H, Totterman K-J, Melander A: Therapeutic equivalence of once- and thrice-daily glipizide. *Eur J Clin Pharmacol* 31:95–99, 1986
8. Karam JH, Sanz N, Salamon E, Nolte MS: Selective unresponsiveness of pancreatic β-cells to acute sulphonylurea stimulation during sulphonylurea therapy in NIDDM. *Diabetes* 35:1314–20, 1986
9. Faber OK, Beck-Nielsen H, Binder C, Butzer P, Damsgaard EM, Froland F, Hjollund E, Lindskow HO, Melander A, Pedersen O, Petersen P, Schwarts Sorensen N, Wahlin-Boll E: Acute actions of sulfonylurea drugs during long-term treatment of NIDDM. *Diabetes Care* 13 (Suppl. 3):26–31, 1990
10. Melander A, Blitzen PO, Faber O, Groop L: Sulphonylurea antidiabetic drugs.

Drugs 37:58–72, 1989
11. Skillman TG, Feldman JM: The pharmacology of sulfonylureas. *Am J Med* 70: 361–72, 1981
12. Jackson JE, Bressler R: Clinical pharmacology of sulphonylurea hypoglycaemic agents: part 1. *Drugs* 22:211–45, 1981
13. Ma A, Kamp M, Bird D, Howlett V, Cameron DP: The effects of long-term gliclazide administration on insulin secretion and insulin sensitivity. *Aust NZ J Med* 19:44–49, 1989
14. Jaber LA, Wenzloff NJ, Komanicky P, Antal EJ: An evaluation of the therapeutic effects and dosage equivalence of glyburide and glipizide. *J Clin Pharmacol* 30:181–88, 1990
15. Kilo C: Multicenter comparison of glyburide and glipizide in the treatment of non-insulin-dependent diabetes mellitus. *Clin Therapeutics* 10:294—302, 1988
16. Scheen AJ, Lefebvre PJ, Luyckx AS: Glipizide increases plasma insulin but not C-peptide level after a standardized breakfast in type 2 diabetic patients: *Eur J Clin Pharmacol* 26:471–74, 1984
17. Matsuda A, Kuzaya T, Sugita Y, Kawashima K: Plasma levels of glibenclamide in diabetic patients during its routine clinical administration determined by a specific radioimmunoassay. *Hormon metabol Res* 15:425–28, 1983
18. Vague P, Moulin JP: The defective glucose sensitivity of the B-cell in non-insulin-dependent diabetes: improvement after twenty hours of normoglycaemia. *Metabolism* 31:139–42, 1982
19. Pfeifer MA, Halter JB, Judewitsch RG, Beard JC, Best JD, Ward WK, Porte D: Acute and chronic effects of sulfonylurea drugs on pancreatic islet function in man. *Diabetes Care* 7 (Suppl. 1):25–34, 1984
20. Sartor G, Melander A, Schersten B, Wahlin-Boll Comparative single—dose kinetics and effects of four sulfonylureas in healthy volunteers. *Acta Med Scand* 208:301–307, 1980
21. Goebel R, Leb G: Effects of glyburide and glipizide on levels of immunoreactive insulin and blood sugar. In *Glipizide. A Worldwide Review*, Excerpta Medica, Princeton NJ 1984, p. 9–15
22. Raptis S, Rau RM, Schroder KE, Faulhaber JD, Pfeiffer EF: Comparative study of insulin secretion following repeated administration of glucose, tolbutamide and glibenclamide (HB419) in diabetic and non-diabetic human subjects. *Hormon Metab Res* 1 (Suppl.):65–72, 1969
23. Haupt E, Koberich W, Beyer J, Schoffling K: Pharmacodynamic aspects of tolbutamide, glibenclamide, glibornuride and glisoxepide. *Diabetologia* 7:449–54, 1971
24. Boyd AE, Aguilar-Bryan L, Nelson DA: Molecular mechanisms of action of glyburide on the β-cell. *Am J Med* 89 (Suppl. 2A):3S-10S, 1990