Comparative Effects of Glibenclamide and Metformin on Ambulatory Blood Pressure and Cardiovascular Reactivity in NIDDM

PURNIMA SUNDARESAN, BSC
DENISE LYKOS, BSC
ALI DAHER
TERENCE DIAMOND, MB, CHB, FRACP
RICHARD MORRIS, MB, BS, FRANZCA
LAURENCE G. HOWES, MB, BS, PHD, FRACP

OBJECTIVE — To compare the effects of chronic glibenclamide and metformin therapy on blood pressure (BP) and cardiovascular responsiveness in patients with NIDDM.

RESEARCH DESIGN AND METHODS — Fourteen patients with NIDDM received metformin or glibenclamide for 1 month in a double-blind, randomized crossover study. At the end of each treatment period, patients were tested for forearm vascular responsiveness to intrabrachial arterial infusion of diazoxide (an ATP-sensitive potassium channel opener), acetylcholine, sodium nitroprusside, and norepinephrine, BP responses to intravenous infusions of NE and angiotensin II, BP responses to cold pressor testing and isometric exercise, and 24-h ambulatory BP monitoring.

RESULTS — Metformin and glibenclamide produced similar glycemic control. Mean 24-h BPs did not differ between the two groups, but mean 24-h heart rates were significantly lower (75 ± 6 bpm vs. 80 ± 6 bpm) on glibenclamide therapy than on metformin. Plasma norepinephrine levels were significantly higher on glibenclamide (6.41 ± 1.77 vs. 4.26 ± 1.54 mmol/l, $P < 0.01$) , and systolic BP responses to intravenous norepinephrine and angiotensin II were significantly higher on glibenclamide than on metformin ($P < 0.02$ and $P < 0.05$, respectively). Systolic BP responses to cold pressor testing appeared higher on glibenclamide than on metformin, but the difference did not quite achieve statistical significance ($P = 0.052$). Baseline forearm vascular resistance did not differ between the two drugs, nor did forearm vascular resistance responses to diazoxide, acetylcholine, sodium nitroprusside, and norepinephrine differ.

CONCLUSIONS — Glibenclamide therapy is accompanied by greater systolic BP responses to norepinephrine and angiotensin II and higher plasma norepinephrine levels than those that occur on metformin therapy. Lower heart rates on glibenclamide therapy despite evidence of greater sympathetic activity suggests that glibenclamide may have negative chronotropic effects.

Interest in the cardiovascular effects of sulfonylureas has grown following the recognition that they may be capable of blocking ATP-sensitive potassium (K_{ATP}) channels in the heart and vascular smooth muscle. An uncontrolled retrospective review of the medical records of 22 patients with NIDDM whose treatments had been changed from insulin to the second-generation sulfonylurea chlorpropamide found that blood pressures (BPs) were higher when the patients were receiving chlorpropamide (1).

In contrast to sulfonylureas, metformin (a commonly used hypoglycemic agent of the biguanide group) has been reported to lower BP in normotensive patients with NIDDM (2); hypertensive, obese, nondiabetic women (3); hypertensive, nondiabetic, nonobese men (4); and normal volunteers (5). However, a large study of metformin treatment in moderately obese patients with NIDDM (6) failed to demonstrate a fall in BP.

To further investigate the comparative cardiovascular effects of sulfonylureas and biguanides, we compared the effects of glibenclamide with those of metformin on 24-h ambulatory BP recordings, BP responses to norepinephrine and angiotensin II, and forearm vascular responses to the intrabrachial artery infusions of vasoconstrictors and vasodilators in patients with NIDDM.

RESEARCH DESIGN AND METHODS

— The study was of a random-order double-blind crossover design comparing the effects of 4 weeks of glibenclamide therapy with 4 weeks of metformin in 14 patients with NIDDM. The subjects (nine men and five women) were aged 40–73 years (mean 60.9 ± 8.8 years) and had baseline glycated hemoglobin levels in the range of 5.7–10% (mean 7.25 ± 0.94%). All 14 subjects provided signed informed consent prior to participation in the study, which was approved by the Southern Sydney Area Health Service Ethics Committee. All subjects had been receiving stable dietary and oral hypoglycemic therapy with sulfonylureas or metformin for at least 3 months before the study, except for one who was treated with dietary therapy alone. None of the subjects was receiving insulin.

Eleven subjects were receiving antihypertensive therapy consisting of ACE inhibitors or calcium-channel blockers. All antihypertensive therapy was kept constant for the duration of the study. Two subjects who were previously receiving lipid-lowering medication ceased taking their lipid-lowering drugs 4 weeks prior to the commencement of the study. All other concomitant medication was kept constant over the 8-week period of the study. The subjects had BMIs that were within 40% of ideal and were all free from detectable complications

From the Department of Clinical Pharmacology (P.S., D.L., A.D., L.G.H.), the Division of Critical Care (R.M.), and the Department of Endocrinology (T.D.), University of New South Wales, St. George Hospital, Kogarah, New South Wales, Australia.

Address correspondence and reprint requests to Laurence G. Howes, PhD, Department of Clinical Pharmacology, St. George Hospital, Kogarah NSW Australia 2217. E-mail: l.howes@unsw.edu.au.

Received for publication 5 September 1996 and accepted in revised form 9 December 1996.

BP, blood pressure; K_{ATP}, ATP-sensitive K^+.

of diabetes, including atherosclerotic vascular disease, retinopathy, macroalbuminuria, and autonomic neuropathy.

The 14 patients were randomized to one of two treatment orders (glibenclamide followed by metformin or metformin followed by glibenclamide) and received each of the two therapies for 4 weeks. There was no placebo washout period prior to commencement or between the two treatment phases as it was considered undesirable to disrupt patients' glycemic control. The initial dose of medication was either 5 mg glibenclamide twice a day or 500 mg metformin twice a day. The subjects' blood glucose levels were monitored throughout the study, and the subjects were reviewed after 2 weeks of each treatment phase. If their fasting blood glucose levels were consistently >8 mmol/l, the dose of medication was doubled to either 10 mg glibenclamide or 1 g metformin twice daily. Subjects were told to maintain their usual diet and keep their physical activity and alcohol intake (<40 g/day) constant over the 8-week study period. Twenty-four–hour ambulatory BP readings, studies of vascular responses to intra-arterial infusions, BP responses to intravenous infusions of pressor agents, cold pressor testing, and isometric exercise, and blood sampling were performed over 2 study days at the end of each treatment phase. The patients abstained from alcohol for 24 h and from caffeine for 12 h before each of the study days.

Day 1

The subjects attended at 9:00 A.M., having consumed a standard light breakfast at 7:00–7:30 A.M. An indwelling cannula was inserted into the median cubital vein of one arm, and after 15 min of supine rest, blood samples were collected for the measurement of glycated hemoglobin (HbA_1) levels, plasma triglyceride and lipoprotein cholesterol levels, plasma insulin, and plasma norepinephrine. After this, the BP responses (measured continuously and indirectly from a finger using a Finapres recorder) to intravenous infusions of progressively increasing concentrations of norepinephrine (0–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and angiotensin II (0–50 $ng \cdot kg^{-1} \cdot min^{-1}$) were measured. The infusions were separated by 30 min of supine rest, after which time BPs had returned to baseline levels. After a further 30 min of supine rest, BP responses to 2 min of isometric exercise were measured, and following a further 30 min of supine rest, a 2-min cold pressor test was performed. Isometric exercise was performed using hand grip at 30% of maximal grip, and cold pressor testing was performed by inserting a hand in ice water. BP was measured continuously from the opposite hand using a Finapres recorder. Baseline BP measurements were taken as the mean of five readings taken at 30-s intervals read from the screen of the Finapres recorder immediately prior to the isometric and cold pressor procedures. The maximum rise in systolic and diastolic BP during each procedure was calculated from the highest instantaneous systolic BP and diastolic BP observed on the screen of the Finapres recorder during the procedure minus the baseline values.

At the end of the first study day, each subject was fitted with a 24-h ambulatory BP monitor (90207, SpaceLabs), programmed to record BPs at 30-min intervals during the day and hourly during the night. The subject was also provided with a bottle for a 24-h urine collection (carried out between the two study days) for measurements of sodium and potassium excretion.

Day 2

The patients attended at 9:00–10:00 A.M., having consumed a standard light breakfast at 7:00–7:30 A.M. An indwelling cannula was inserted into the brachial artery after the ambulatory blood pressure monitor had been removed. After baseline measurements of forearm blood flow were taken, vascular responses to infusions of nitroprusside (0.2–1.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$), norepinephrine (25–100 $ng \cdot kg^{-1} \cdot min^{-1}$), acetylcholine (3–24 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and diazoxide (3.75–30 $mg \cdot kg^{-1} \cdot min^{-1}$) were measured using venous occlusion plethysmography (Hokanson EC 4). We did not use a control arm because the changes in basal forearm vascular resistance values within study days were insignificant (<5%) compared with the changes that occurred in response to infusions of the vasoactive substances and because the amounts of drug infused were, in our experience, too small to produce measurable systemic effects. Furthermore, the contralateral arm was required for accurate brachial BP measurements to allow the calculation of changes in forearm vascular resistance. These measurements were made using a SpaceLabs ambulatory monitor at 1-min intervals during the infusions. The infusions were separated by 15 min of supine rest, by which time the forearm vascular resistance had returned to baseline levels.

Statistical analysis

For the analysis of data from the measurements of vascular responses and BP responses, an analysis of variance model was used, with drug treatment and repeated measurements of the parameters of interest on each study day as dependent variables and treatment order as an independent variable. Post hoc pairwise comparisons were also carried out using the Neuman-Keuls test. Analysis of 24-h BP data was by repeated measures analysis of variance to extract treatment and time effects and treatment order and treatment time interactions. Differences in the rise in systolic BP and diastolic BP during isometric exercise and cold pressor testing, and differences in blood glucose, glycated hemoglobin, insulin levels, norepinephrine levels, lipoprotein cholesterol and triglyceride levels, and 24-h urinary electrolyte excretion were analyzed using paired Student's *t* tests. All values were expressed as means ± SD.

Drugs

Glibenclamide and metformin were supplied by Alphapharm (Sydney, Australia). Matching placebos were made by Medical Research (Parramatta, Australia). Norepinephrine (Levophed 1:1,000, Winthrop, Ermington, Australia), angiotensin II (Angiotensin II Human, Sigma, St. Louis, MO), nitroprusside (Sodium Nitroprusside for Injection BP, David Bull Laboratories, Melbourne, Australia), acetylcholine (Miochol, Johnson & Johnson, Sydney, Australia), and diazoxide (Diazoxide for Injection BP, David Bull Laboratories, Melbourne, Australia) were diluted under sterile conditions with normal saline except for nitroprusside, which was diluted with 5% glucose solution.

RESULTS

Glycemic control

The mean doses of the drugs were 1,214 ± 426 mg/day of metformin and 12.14 ± 4.26 mg/day of glibenclamide. At the end of the metformin treatment phase, the mean glycated hemoglobin level was 7.73 ± 1.58%; at the end of the glibenclamide treatment phase, it was 8.01 ± 1.61%, which indicates that the glycemic control achieved during both treatment phases was similar ($P = 0.91$). Glycated hemoglobin levels at the end of each treatment phase were significantly higher ($P < 0.05$) than screening values. Fasting blood glucose concentrations taken on the study days were available for

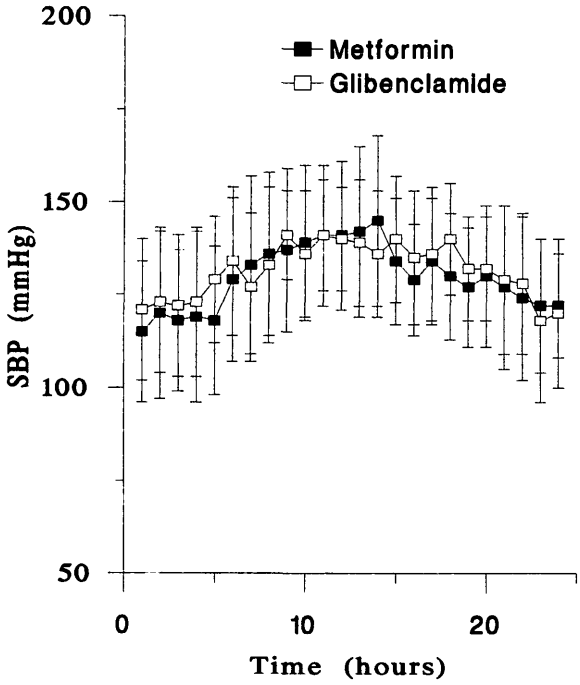

Figure 1—*Twenty-four–hour systolic BP (SBP) profiles during metformin therapy and glibenclamide therapy. There were no significant differences between the BP profiles on each treatment (repeated measures analysis of variance).*

eight patients, and analysis of these showed no significant difference between the blood glucose values obtained during the two phases (metformin 6.92 ± 3.17 mmol/l and glibenclamide 7.21 ± 2.44 mmol/l, P = 0.46). Body weight did not differ significantly between the two treatment phases (metformin 73.2 ± 10.4, glibenclamide 73.5 ± 10.7 kg, P = 0.84).

BP and heart rate

Analysis of 24-h BP data (Fig. 1) showed no difference in the mean 24-h BPs between the two treatment phases (metformin 130 ± 22 / 77 ± 16 mmHg and glibenclamide 131 ± 20 / 75 ± 13 mmHg). However, mean 24-h heart rates were significantly lower on glibenclamide (75 ± 6 bpm) than on metformin (80 ± 6 bpm) ($P < 0.01$). Exclusion of the three patients who were not receiving antihypertensive therapy from the analysis did not alter these results.

BP responses to intravenous norepinephrine and angiotensin II

Figure 2 shows the systolic BP responses to the norepinephrine infusions during the two treatment periods. Systolic BP responses to the intravenous infusions of norepinephrine were significantly higher on glibenclamide treatment than on metformin treatment ($P < 0.02$, drug vs. infusion concentration interaction). Diastolic BPs increased significantly during norepinephrine infusions ($P < 0.001$). While the increase in diastolic BP at the highest norepinephrine infusion rate appeared higher on glibenclamide than on metformin (10 ± 4 vs. 7 ± 7 mmHg), the differences between the dose-response curves were not statistically significant ($P = 0.21$).

The BP responses to intravenous angiotensin II infusions (Fig. 2) showed a significantly higher systolic BP response during glibenclamide treatment compared with metformin treatment ($P < 0.05$). Diastolic BPs increased significantly during angiotensin II infusions ($P < 0.001$). Although the increase in diastolic BP at the highest angiotensin II infusion rate appeared higher on glibenclamide than on metformin (18 ± 10 vs. 6 ± 7 mmHg), the differences between the dose-response curves were not statistically significant ($P = 0.51$).

Exclusion of the three patients who were not receiving antihypertensive therapy from the analysis did not alter these results.

BP responses to cold pressor and isometric exercise testing

Systolic BP in response to cold pressor testing increased to a greater extent on glibenclamide (46 ± 22 mmHg) than on metformin therapy (34 ± 16 mmHg), but the difference did not quite achieve statistical significance (mean difference 11 ± 18 mmHg, $P = 0.052$). Diastolic BP responses to cold pressor testing were similar on glibenclamide (24 ± 12 mmHg) and metformin (20 ± 12 mmHg) ($P = 0.42$).

Systolic BP responses to isometric exercise testing were similar on glibenclamide (34 ± 18 mmHg) and metformin (39 ± 14 mmHg) ($P = 0.46$). Diastolic BP responses to isometric exercise testing were also similar on glibenclamide (23 ± 22 mmHg) and metformin (24 ± 12 mmHg) ($P = 0.85$).

Plasma norepinephrine and insulin levels

Norepinephrine levels were significantly higher during glibenclamide treatment (6.41 ± 1.77 mmol/l) than during metformin therapy (4.26 ± 1.54 mmol/l) ($P < 0.01$).

Insulin levels varied greatly between subjects during glibenclamide treatment and between study days and did not differ significantly between glibenclamide and metformin therapy (glibenclamide 34.44 ± 26.89 mU/l, metformin 15.79 ± 8.65 mU/l), although values tended to be higher on glibenclamide ($P = 0.18$).

Forearm vascular resistance studies

There were no significant differences in the baseline forearm vascular resistance between the metformin and glibenclamide treatment phases (glibenclamide 126 ± 53 × 10^5, metformin 120 ± 69 × 10^5 dynes · s · cm^{-5}) ($P = 0.57$).

The dose-response curves for the intrabrachial artery infusions of nitroprusside, acetylcholine, diazoxide, and norepinephrine are shown in Fig. 3. There were no significant differences between glibenclamide and metformin therapies in the vascular responses to these substances.

Lipoprotein profiles, 24-h electrolyte excretion

Plasma lipoprotein profiles did not differ significantly between the metformin and glibenclamide treatment phases (total cholesterol: glibenclamide 6.16 ± 1.12 and metformin 6.24 ± 1.02 mmol/l; triglyceride: glibenclamide 3.23 ± 1.27 and metformin 3.14 ± 1.04 mmol/l; HDL: glibenclamide 0.95 ± 0.26 and metformin 0.98 ± 0.35 mmol/l; LDL: glibenclamide 4.19 ± 0.89 and metformin 3.82 ± 0.8 mmol/l).

There were no significant differences in the 24-h excretion of sodium (metformin 196 ± 106 mmol/day, glibenclamide 187 ± 66 mmol/day, $P = 0.79$) or potassium (metformin 74 ± 21 mmol/day, glibenclamide

76 ± 10 mmol/day, $P = 0.79$) between the two treatment phases.

Treatment order interactions

Treatment order did not significantly influence any of the study results.

CONCLUSIONS — The present study has demonstrated that 4 weeks of glibenclamide treatment is associated with greater systolic BP responses to intravenous infusions of norepinephrine and angiotensin II, a borderline increase in systolic BP responses to cold pressor testing, and elevated plasma norepinephrine levels compared with metformin. The increased systolic BP reactivity to pressor stimuli occurred in the absence of an enhanced forearm vascular resistance response to intrabrachial arterial norepinephrine. This suggests that the altered BP responses were not mediated by changes in peripheral resistance vessels, at least not at forearm resistance vessels, and may to an extent reflect increased cardiac responsiveness. Diastolic BP responses to norepinephrine and angiotensin II were numerically higher on glibenclamide than on metformin, but the differences were not statistically significant. The reason for the greater systolic BP responsiveness to norepinephrine and angiotensin II during glibenclamide therapy is unclear.

The greater reactivity to the exogenous pressor agents during glibenclamide therapy may have been due to greater levels of sympathetic activity, indicated by higher plasma norepinephrine levels. However, if this was the case, the difference in sympathetic activity between the two drug therapies did not appear to involve all vascular beds, as no potentiation of the vasoconstrictor effects of norepinephrine was observed in the forearm. Furthermore, this hypothesis does not readily explain the increased BP responsiveness to angiotensin II observed during glibenclamide therapy, except perhaps via presynaptic facilitation of norepinephrine release by angiotensin II (7).

It is possible that the difference in sympathetic activity between glibenclamide and metformin therapy was secondary to differences in insulin secretion. There is evidence that chronic sulfonylurea therapy increases plasma insulin levels in NIDDM patients (8), while metformin therapy may decrease insulin levels (3). Short-term intravenous and intra-arterial infusions of insulin in normal volunteers and borderline hypertensive subjects (9) have been shown to increase forearm blood flow (9,10), increase plasma norepinephrine levels (10), and decrease forearm blood flow responses to intrabrachial artery infusions of norepinephrine and angiotensin II (11) while having small and variable effects on BP and heart rate (9,10,12). The effects on the cardiovascular and sympathetic nervous system of chronic insulin administration in humans are unknown, and the acute vasodilator effects of insulin in the presence of antihypertensive therapy are uncertain. However, chronic administration of insulin to rats has been reported to elevate BP and cause sympathetic activation (13). Insulin levels did not differ significantly between glibenclamide and metformin therapy in the present study. However, only one measurement was made during each treatment phase, and few attempts were made to measure them under standardized conditions. Further studies are required to investigate the relationship between changes in insulin secretion and sympathetic activity during sulfonylurea therapy.

The observation that BP responsiveness to norepinephrine and angiotensin II was higher on glibenclamide than on metformin therapy, while the changes in forearm blood flow to norepinephrine did not differ, suggests that the two drugs (or the changes in plasma insulin levels induced by them) may have led to selective changes in adrenoceptor responsiveness or sympathetic outflow in different locations in the cardiovascular system. For example, glibenclamide therapy may have been accompanied by a greater sympathetic outflow to the heart, which could have led to a greater inotropic response to exogenous norepinephrine because of a net increase in the amount of norepinephrine at cardiac β-receptors. However, an increase in cardiac sympathetic activity on glibenclamide compared with metformin would be expected to be accompanied by an increase in heart rate. In contrast, we found that heart rates were lower on glibenclamide therapy than on metformin. This suggests that glibenclamide may have direct negative chronotropic effects, possibly because of effects on cardiac K_{ATP} channels (14), or may have increased vagal tone either reflexly or via uncharacterized mechanisms. It is possible that glibenclamide therapy was associated with vasoconstriction and a greater response to norepinephrine in vascular beds that we did not study, such as the splanchnic and renal circulations, and that a reflex reduction in heart rate occurred on glibenclamide compared with metformin because of a higher level of total peripheral resistance. Chan et al. (2) demonstrated an

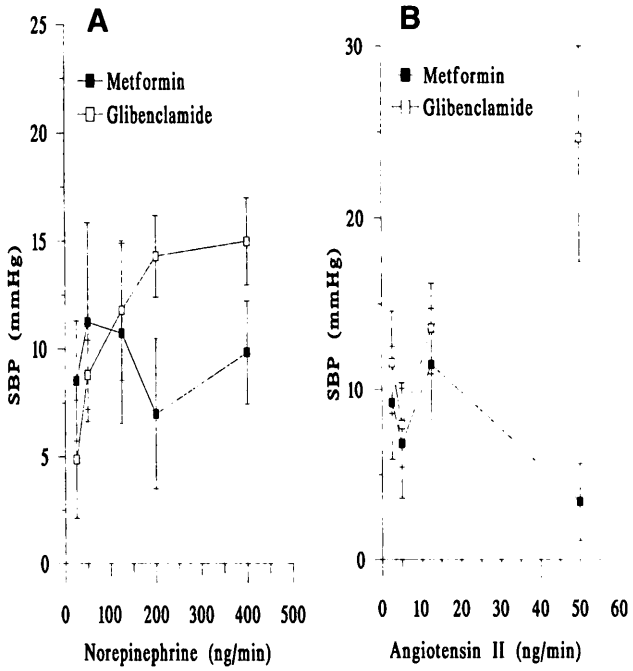

Figure 2—*Systolic BP (SBP) responses to norepinephrine (A) and angiotensin II (B) on metformin and on glibenclamide therapy. SBP responses were significantly greater on glibenclamide therapy than on metformin therapy for both norepinephrine ($P < 0.02$) and angiotensin II ($P < 0.05$) (repeated measures analysis of variance, drug vs. infusion rate interaction).*

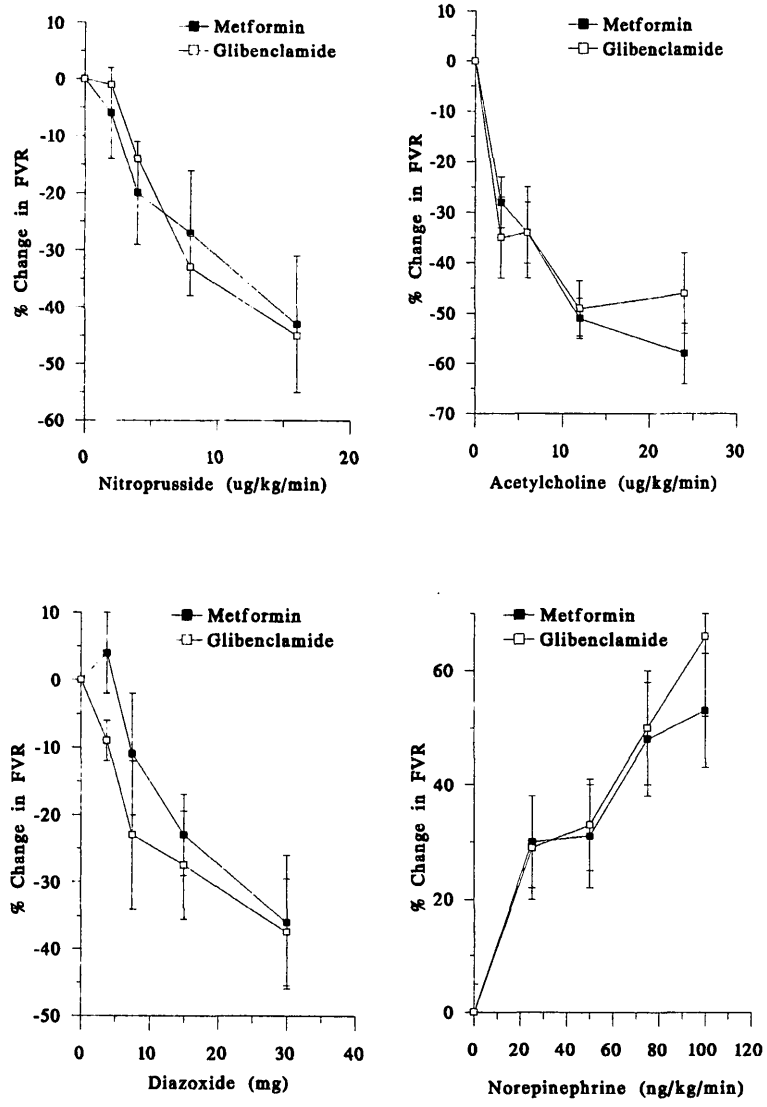

Figure 3—*Forearm vascular resistance (FVR) responses to nitroprusside, acetylcholine, diazoxide, and norepinephrine on metformin and on glibenclamide therapy. There were no significant differences in the responses to any of these vasoactive substances in the forearm between metformin and glibenclamide therapy.*

increase in systemic vascular resistance following 4 weeks of glibenclamide therapy compared with metformin therapy. It is also possible that glibenclamide increased sympathetic activity via mechanisms that have not yet been characterized, such as effects on central K_{ATP} channels, or that metformin suppressed sympathetic activity through unknown mechanisms. An increase in sympathetic activity would generally be expected to lead to postsynaptic receptor downregulation and a reduced sensitivity to exogenous catecholamines, rather than the increase observed in the present study. It is possible that the increase in sympathetic activity on glibenclamide therapy was associated with an additional and possibly unrelated increase in postsynaptic responsiveness to norepinephrine and angiotensin II.

Systolic BP responses to cold pressor testing were higher on glibenclamide than on metformin, but the difference was of borderline significance. This result is consistent with the greater systolic BP responsiveness to exogenous vasopressor agents. In contrast, no significant differences in the diastolic BP responses to isometric exercise or diastolic BP responses to cold pressor testing.

It is possible that patients receiving different antihypertensive drugs respond to the cardiovascular effects of metformin and glibenclamide in different ways. Further studies would be required to establish this possibility.

If the effects of glibenclamide on plasma norepinephrine levels and BP responses to intravenous infusions of norepinephrine and angiotensin II are mediated by changes in insulin release, it remains to be established whether or not they persist with longer duration of therapy. A 4-week treatment period with glibenclamide may not have been long enough to result in the stabilization of insulin levels.

In conclusion, the present study has demonstrated that systolic responsiveness to intravenous norepinephrine and angiotensin II infusions is increased during chronic glibenclamide therapy compared with metformin therapy without alterations in local forearm vascular responses, and that plasma norepinephrine levels are also elevated. The results suggest that glibenclamide therapy is associated with greater sympathetic nervous system activity and pressor responsiveness to norepinephrine and angiotensin II compared with metformin therapy. Despite the differences in sympathetic activity and vascular responsiveness between the two drugs, mean 24-h ambulatory BPs did not differ significantly between glibenclamide and metformin therapy, and heart rates were lower on glibenclamide. Further placebo-controlled studies are required to clarify the mechanisms leading to the differences in sympathetic activity and vascular responsiveness between glibenclamide and metformin therapy.

References

1. Schmidtt J, Moore J: Hypertension secondary to chlorpropamide with amelioration by changing to insulin. *Am J Hypertens* 6:317–319, 1993
2. Chan J, Tomlinson B, Critchley J, Cockram C, Walden R: Metabolic and hemodynamic effects of metformin and glibenclamide in normotensive NIDDM patients. *Diabetes Care* 16:1035–1038, 1993
3. Giugliano D, DeRosa N, DiMaro G, Marfella R, Acampora R, Buoninconti R, D'Onofrio F: Metformin improves glucose, lipid metabolism and reduces blood pressure in hypertensive, obese women. *Diabetes Care* 16:1387–1390, 1993
4. Landin K, Tengborn L, Smith U: Treating

insulin resistance in hypertension with metformin reduces both blood pressure and metabolic risk factors. *J Intern Med* 229:181–187, 1991
5. Kelly J, Pham H, Martin A, Whitworth J: Metabolic and hemodynamic effects of short term metformin administration in normotensive men (Abstract). *Am J Hypertens* 8:134a, 1995
6. DeFronzo R, Goodman A, Groop M: Efficacy of metformin in patients with non-insulin dependent diabetes mellitus. *N Engl J Med* 333:541–549, 1995
7. McGrath B, Oliver J, Moguilevski V, Trigg L, Akama H, Shimizu K: Noradrenaline spillover to exercise muscle is increased and facilitated by angiotensin II in normal but not in heart failure rabbits (Abstract). *High Blood Pressure Research Council of Australia Proceedings, Melbourne, Australia, 1995*. p. 48
8. Ma A, Kamp M, Bird D, Howlett V, Cameron DP: The effects of long term gliclazide administration on insulin secretion and insulin sensitivity. *Aust N Z J Med* 19:44–49, 1989
9. Anderson E, Balon T, Hoffman R, Sinkey C, Mark A: Insulin increases sympathetic activity but not blood pressure in borderline hypertensive humans. *Hypertension* 19:621–627, 1992
10. Anderson E, Hoffman R, Balon T, Sinkey C, Mark A: Hyperinsulinemia produces both sympathetic neural activation and vasodilation in normal humans. *J Clin Invest* 87:2246–2252, 1991
11. Sakai K, Imaizumi T, Masaki H, Takeshita A: Intra-arterial infusion of insulin attenuates vasoreactivity in human forearm. *Hypertension* 22:67–73, 1993
12. Rooney DP, Edgar JD, Sheridan B, Atkinson AB, Bell PM: The effects of low dose insulin infusions on the renin angiotensin and sympathetic nervous systems in normal man. *Eur J Clin Invest* 21:430–435, 1991
13. Bunag RD, Krizsan-Agbas D, Itoh H: Sympathetic activation by chronic insulin treatment in conscious rats. *J Pharmacol Exp Ther* 259:131–138, 1991
14. Bril A, Laville M, Gout B: Effects of glibenclamide on ventricular arrhythmias and cardiac function in ischaemia and reperfusion in isolated rat heart. *Cardiovasc Res* 26:1069–1076, 1992