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Effects of glimepiride and glyburide on glucose counterregulation and recovery from hypoglycemia

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Abstract

Severe hypoglycemia, the most serious side effect of sulfonylurea therapy, has been reported to occur more frequently with glyburide than glimepiride. The present studies were undertaken to test the hypothesis that a differential effect on glucagon secretion may be involved. We performed hyperinsulinemic hypoglycemic (~2.5 mmol/L) clamps in 16 healthy volunteers who received in randomized order placebo, glyburide (10 mg), and glimepiride (4 mg) just before beginning the insulin infusion and measured plasma glucagon, insulin, C-peptide, glucagon, epinephrine, cortisol, and growth hormone levels during the clamp and during a 3-hour recovery period after discontinuation of the insulin infusion. Neither sulfonylurea altered glucagon responses or those of other counterregulatory hormones (except cortisol) during the clamp. However, glyburide delayed plasma glucose recovery from hypoglycemia (plasma glucose at end of recovery period: control, 4.9 ± 0.2 mmol/L; glyburide, 3.7 ± 0.2 mmol/L; $P = .0001$; glimepiride, 4.5 ± 0.2 mmol/L; $P = .08$). Despite lower plasma glucose levels, glyburide stimulated insulin secretion during this period (0.89 ± 0.13 vs 1.47 ± 0.15 pmol · kg^{-1} · min^{-1}, control vs glyburide; $P = .001$), whereas glimepiride did not ($P = .08$). Short-term administration of glyburide or glimepiride did not alter glucagon responses during hypoglycemia. In contrast, during recovery from hypoglycemia, glyburide but not glimepiride inappropriately stimulates insulin secretion at low plasma glucose levels. This differential effect on insulin secretion may be an important factor in explaining why glyburide causes severe hypoglycemia more frequently than glimepiride.

1. Introduction

Sulfonylureas are commonly used to treat type 2 diabetes mellitus. Their most serious side effect is hypoglycemia [1], which often is an impediment for achieving optimal glycemic control [2].

The frequency of severe hypoglycemia varies considerably among sulfonylureas [3]. Potency and duration of action have generally been considered the most important factors [4]. However, despite the fact that glyburide and glimepiride have roughly similar efficacies and durations of action [1,5], the frequency of severe hypoglycemia appears to be several-fold greater in patients treated with glyburide than those treated with glimepiride [6]. Thus, some factor(s) other than potency and duration of action may be important [7].

In addition to different actions on pancreatic beta cells [8-10], a differential effect on pancreatic alpha cells is a possibility. Pancreatic alpha cells, such as pancreatic beta cells, contain sulfonylurea receptors linked to K-ATP–sensitive potassium channels [11-15]. After the demonstration by Samols et al [16] of a suppressive effect of tolbutamide on plasma glucagon in ducks, numerous in vitro studies have shown an inhibitory effect of several sulfonylureas (gliclazide, glyburide, tolazamide, and tolbutamide) on glucagon secretion [17-19,19-22]. In contrast, glimepiride has not been found to affect glucagon secretion in vitro [23].

In human studies, long-term sulfonylurea treatment with tolazamide, chlorpropamide, tolbutamide, or acetohexamide has been reported to suppress postprandial glucagon

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secretion in patients with type 2 diabetes mellitus [24]. Moreover, both tolbutamide [25] and glyburide [26,27] have been reported to reduce glucagon responses to hypoglycemia. However, no data are currently available on the effects of glimepiride in human beings.

We therefore undertook these studies to test the hypothesis that suppression of the glucagon response to hypoglycemia by glyburide but not by glimepiride might be an important factor explaining the difference in frequency of severe hypoglycemia with these 2 sulfonylureas. In addition, we compared insulin secretory kinetics and the responses of other counterregulatory hormones (growth hormone, epinephrine, and cortisol) during a 2-hour hyperinsulinemic hypoglycemic (~2.45 mmol) clamp experiment and during a 3-hour recovery period.

2. Research design and methods

2.1. Subjects

Informed written consent was obtained from 16 healthy volunteers (6 men and 10 women) after the protocol had been approved by the University of Rochester Institutional Review Board. Subjects were 40 ± 3 years and had a body mass index of 27 ± 1 kg/m^2. Their screening history, physical examination, and routine laboratory tests (hemoglobin A_{1c}, metabolic profile, lipid panel, thyroid-stimulating hormone, complete blood count, and urinalysis) were normal.

2.2. Protocol

All subjects were studied on 3 occasions, separated by at least 1 week: on the first occasion, all subjects were studied with placebo. On the second and third occasions, the subjects were randomized to ingest either 10 mg of glyburide or 4 mg of glimepiride approximately 5 minutes before the start of a standard hyperinsulinemic hypoglycemic clamp experiment [28-30].

For each study, subjects were admitted to the University of Rochester General Clinical Research Center between 5:00 and 6:00 PM the evening before experiments, received a standard dinner (41.84 kJ/kg: 50% carbohydrate, 35% fat, 15% protein) between 6:30 and 7:00 PM, and fasted thereafter except for water until the experiments were completed.

At approximately 7:00 AM the following morning, a retrograde venous catheter was inserted into a dorsal hand vein, and the hand was kept in a thermoregulated Plexiglass box at 65°C for sampling arterialized venous blood [31]. A contralateral antecubital vein was cannulated for infusions. At 8:00 (−30 minutes) and 8:30 AM (0 minute), baseline blood samples for plasma insulin, glucagon, C-peptide, epinephrine, growth hormone, cortisol, and glucose were collected. At 8:25 AM (−5 minutes), a standard pill containing placebo, glimepiride, or glyburide was given; after which, a continuous infusion of insulin (1.5 mU · kg^{-1} · min^{-1}) was begun, and plasma glucose concentrations were allowed to decrease to 45 to 50 mg/dL (2.5-2.8 mmol/L) during the following 120 minutes using the glucose clamp technique [28]. At 120 minutes, the insulin infusion was stopped, and plasma glucose was allowed to recover over the next 3 hours. Glucose was infused only if the blood glucose failed to rise above 50 mg/mL. Blood samples were collected every 15 minutes during the clamp and every 20 minutes during the recovery period (180 minutes) for measurement of plasma insulin, glucagon, C-peptide, epinephrine, growth hormone, cortisol, and glucose.

2.3. Analytical procedures

Blood samples were collected for plasma insulin, C-peptide, glucagon, cortisol, and growth hormone in EDTA tubes containing a protease inhibitor and for plasma epinephrine in EGTA tubes. Plasma glucose was immediately determined in duplicate with a glucose analyzer (Yellow Springs Instrument, Yellow Springs, OH). For other determinations, samples were placed immediately in a 4°C ice bath, and plasma was subsequently separated by centrifugation at 4°C. Plasma insulin, C-peptide, glucagon, growth hormone, and cortisol concentrations were determined by standard radioimmunoassays, and plasma epinephrine concentrations were measured by a radioenzymatic method as previously described [32,33].

2.4. Calculations

Rates of insulin secretion were calculated by deconvolution analysis of plasma C-peptide using an open 2-compartmental model [34,35] and population-based transition coefficients [36] as described by Hovorka and Jones [37].

2.5. Statistical analyses

Unless stated otherwise, data are expressed as means ± SEM. Paired 2-tailed Student t tests were used to compare corresponding data of both sets of experiments. A P value of less than .05 was considered statistically significant.

3. Results

3.1. Plasma glucose and insulin concentrations

Baseline plasma glucose and insulin concentrations were comparable in all experiments. During the 120-minute insulin infusion, plasma insulin increased to comparable levels, and plasma glucose was clamped at virtually identical levels in each experiment (~2.5 mmol/L). After stopping the insulin infusion, plasma glucose increased in all experiments but less with glyburide. Values at the end of the recovery period (3 hours after stopping the insulin infusion) were 3.7 ± 0.2 mmol/L in glyburide experiments compared with 4.9 ± 0.2 mmol/L in control experiments ($P < .0001$) and 4.5 ± 0.2 mmol/L in glimepiride experiments ($P < .01$). Values in glimepiride experiments

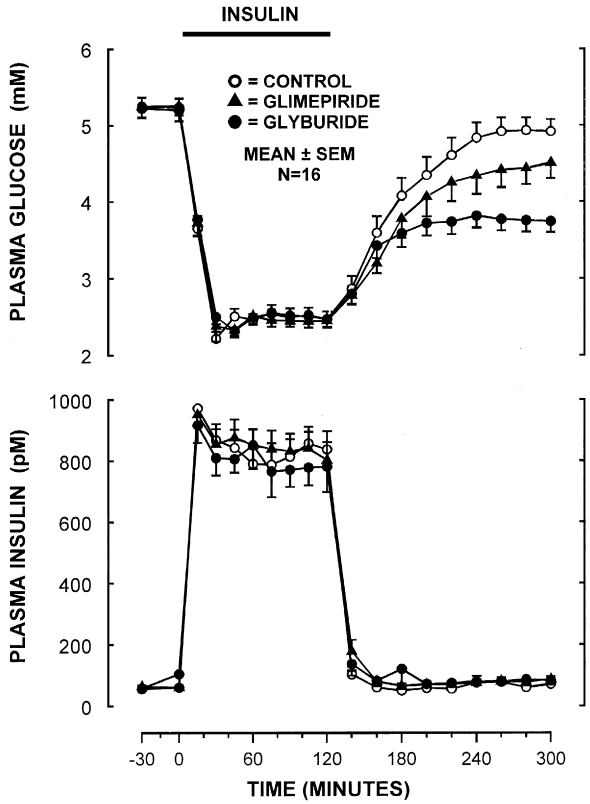

Fig. 1. Plasma glucose and insulin concentrations.

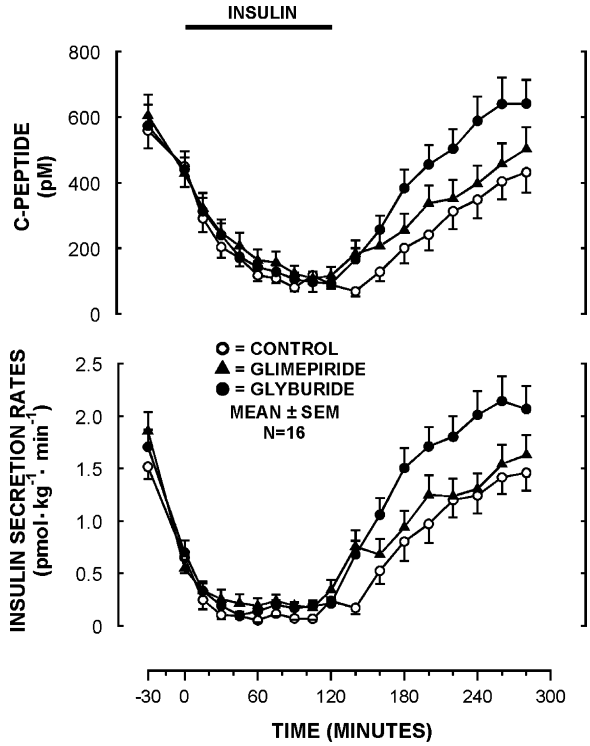

Fig. 2. Plasma C-peptide and insulin secretory rates.

were not significantly different from those in control experiments (P = .08) (Fig. 1, Table 1).

3.2. Plasma C-peptide and insulin secretion rates

Baseline plasma C-peptide concentrations and insulin secretion rates were comparable in all experiments. During the last hour of the hypoglycemic clamp, plasma C-peptide levels were significantly greater in glyburide and glimepiride experiments than in control experiments (P = .05 and .025, respectively). Similarly, insulin secretion rates were significantly greater in glyburide and glimepiride experiments than in control experiments (P = .03 and .01, respectively). Insulin secretion was suppressed 95.2% ± 0.9% in control experiments vs 89.8% ± 1.6% and 89.5% ± 1.5% in glyburide and glimepiride experiments (P = .007 and .008, respectively) (Figs. 2 and 3, Table 1).

After discontinuation of the insulin infusion, plasma C-peptide and insulin secretion rates increased in all

Table 1
Plasma glucose, insulin, and C-peptide concentrations, and insulin secretory rates during the last hour of the hypoglycemic clamp and the subsequent recovery period

	Clamp	P^a	Recovery	P^a
Plasma glucose (mmol/L)				
Control	2.51 ± 0.10		4.34 ± 0.16	
Glyburide	2.51 ± 0.09	.93	3.59 ± 0.13	.001
Glimepiride	2.45 ± 0.08	.44	3.97 ± 0.19	.06
Plasma insulin (pmol/L)				
Control	819 ± 51		68 ± 6	
Glyburide	789 ± 61	.36	84 ± 8	.04
Glimepiride	828 ± 56	.91	87 ± 9	.05
Plasma C-peptide (pmol/L)				
Control	93 ± 13		247 ± 41	
Glyburide	118 ± 18	.05	416 ± 52	.001
Glimepiride	134 ± 27	.025	311 ± 49	.04
Insulin secretory rate (pmol · kg^{-1} · min^{-1})				
Control	0.08 ± 0.01		0.89 ± 0.13	
Glyburide	0.17 ± 0.04	.03	1.47 ± 0.15	.001
Glimepiride	0.20 ± 0.04	.01	1.07 ± 0.14	.08

Data are presented as mean ± SEM.
[a] P vs control.

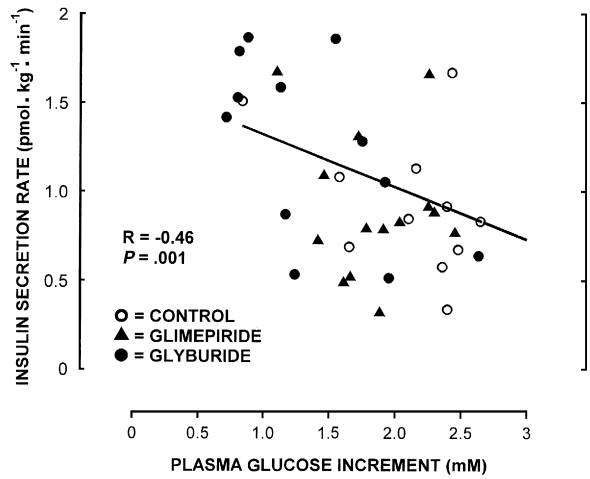

Fig. 3. Correlation between insulin secretory rates and increments in plasma glucose during the 3-hour recovery period after stopping the insulin infusion.

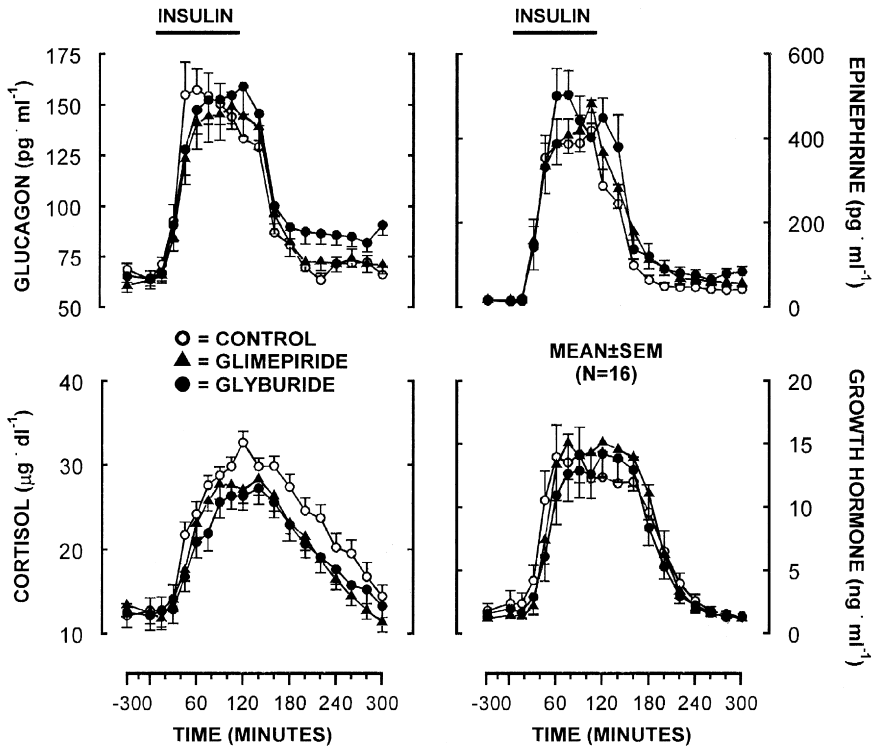

Fig. 4. Plasma glucagon, epinephrine, cortisol, and growth hormone concentrations.

experiments, but increased to a much greater extent in glyburide experiments than in glimepiride (both $P = .001$) and control experiments ($P = .001$ and .002, respectively). Insulin secretory rates in glimepiride and control experiments were not significantly different ($P = .08$).

Increases in plasma glucose during the recovery period were inversely correlated to insulin secretory rates during this period ($r = -0.46$, $P = .002$).

3.3. Counterregulatory hormone responses

Baseline plasma glucagon, cortisol, epinephrine, and growth hormone concentrations were comparable in all experiments. During the hypoglycemic clamps, all plasma counterregulatory hormone concentrations increased comparably except cortisol whose levels were significantly lower in both glyburide ($P = .004$) and glimepiride experiments ($P = .01$), which were not significantly different from one another ($P = .42$) (Fig. 4, Table 2).

During the 3-hour recovery period, plasma cortisol was lower in both glyburide ($P = .047$) and glimepiride ($P = .042$) experiments than in control experiments, but was not significantly different from one another ($P = .17$). Plasma growth hormone concentrations were comparable in all experiments. In contrast, both plasma glucagon and epinephrine concentrations were greater in glyburide experiments than in control experiments ($P = .006$ and .03, respectively); in glimepiride experiments, plasma glucagon and epinephrine responses were not significantly different from those in control experiments ($P = .32$ and .12).

Because plasma glucose levels differed during the recovery period, the appropriateness of the counterregulatory hormone responses was assessed as the product of the plasma glucose and counterregulatory hormone levels. Only plasma glucose cortisol products were different among experiments, being lower with both glyburide and glimepiride ($P = .0002$ and .001, respectively). Glucose infusion rates during the clamps and during the recovery period were not significantly different among experiments (data not shown).

Table 2
Plasma counterregulatory hormones during the last hour of the hypoglycemic clamps and the subsequent recovery period

	Clamp	P^a	Recovery	P^a
Plasma glucagon (pg/mL)				
Control	146 ± 10		79 ± 4	
Glyburide	155 ± 12	.30	95 ± 6	.006
Glimepiride	146 ± 11	.98	83 ± 5	.32
Plasma epinephrine (pg/mL)				
Control	371 ± 54		75 ± 11	
Glyburide	449 ± 50	.11	125 ± 20	.03
Glimepiride	416 ± 37	.43	108 ± 17	.12
Plasma growth hormone (ng/mL)				
Control	12.9 ± 21		5.6 ± 0.9	
Glyburide	13.0 ± 2.0	.95	5.5 ± 0.8	.83
Glimepiride	14.7 ± 2.4	.16	6.1 ± 0.9	.44
Plasma cortisol (μg/dL)				
Control	29.7 ± 1.0		22.9 ± 1.3	
Glyburide	26.1 ± 1.1	.004	20.7 ± 1.3	.047
Glimepiride	27.1 ± 1.4	.01	19.2 ± 1.3	.042

Data are presented as mean ± SEM.
[a] P vs control.

4. Discussion

We found that neither glyburide nor glimepiride affected plasma glucagon, epinephrine, and growth hormone responses during hypoglycemia. However, both sulfonylureas caused a modest (~10%) reduction in plasma cortisol responses. Previous studies have not found sulfonylureas to affect epinephrine and cortisol responses [26,27,38], whereas one study, but not others, found reduced growth hormone responses [39]. The reason for these discrepancies and their clinical significance is unclear.

Both glyburide and glimepiride comparably and modestly reduced suppression of insulin secretion during hypoglycemia (~90% vs 96%). However, it is during the recovery period when the sulfonylureas differed significantly. During this 3-hour interval, plasma glucose increased less with glyburide than with glimepiride. Moreover, despite lower plasma glucose levels with glyburide, insulin secretory rates were 40% greater with this sulfonylurea than with glimepiride and 65% greater than in control experiments. Plasma glucose levels and insulin secretory rates with glimepiride were not significantly different from those in control experiments.

During the recovery period, plasma growth hormone was comparable in all experiments, whereas plasma glucagon and epinephrine were increased in glyburide but not glimepiride experiments. However, these increases in plasma glucagon and epinephrine appeared to be appropriate for the lower plasma glucose levels in glyburide experiments because plasma glucose–epinephrine and plasma glucose–glucagon products were similar in all 3 experiments. Plasma cortisol responses were modestly (~10%-15%) but significantly (P = .045) reduced with both glyburide and glimepiride. The clinical significance of this is unclear. Because cortisol responses were reduced to a comparable extent with each sulfonylurea, these do not explain the differences in plasma glucose recovery.

Our results thus suggest that a main reason for differences in the frequency of severe hypoglycemia between glyburide and glimepiride is their effects on insulin secretion: glyburide caused persistent insulin secretion despite hypoglycemia, whereas glimepiride did not. This conclusion is supported by the fact that increases in plasma glucose during recovery from hypoglycemia were inversely related to insulin secretory rates (Fig. 3).

Glyburide is known to accumulate in islet beta cells, whereas other sulfonylureas do not [8]. Furthermore, in studies using the isolated perfused rat pancreas, stimulation of insulin release persists after discontinuation of glyburide, whereas stimulation by other sulfonylureas generally stops when their infusion is stopped [23,40].

The differences between glyburide and glimepiride on insulin secretion do not appear to be explicable by their different durations of action or the doses used. Both sulfonylureas were administered as half their recommended maximal doses, which probably produce near maximal clinical effects [7,41]. With respect to duration, after oral administration, plasma levels of both sulfonylureas peak at 2 to 4 hours [1,41]. Because glimepiride has a half-life of approximately 5 hours and glyburide has a half-life of approximately 10 hours, plasma levels of both sulfonylureas were expected to have been in the therapeutic range throughout the whole duration of our 6-hour experiment [1,41,42].

In conclusion, our results indicate that short-term administration of glyburide or glimepiride did not alter glucagon responses during hypoglycemia. In contrast, during recovery from hypoglycemia, glyburide but not glimepiride inappropriately stimulated insulin secretion at low plasma glucose levels. We therefore conclude that this differential effect on insulin secretion may be an important factor in explaining why glyburide causes more frequent severe hypoglycemia than glimepiride.

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