Low-Dose Ethanol Predisposes Elderly Fasted Patients With Type 2 Diabetes to Sulfonylurea-Induced Low Blood Glucose

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OBJECTIVE — It has previously been demonstrated that the risk of hypoglycemia is low among otherwise healthy elderly fasted patients with type 2 diabetes taking oral sulfonylurea medications. Nevertheless, these agents do cause hypoglycemia in clinical practice, suggesting that accompanying factors must typically be present for hypoglycemia to occur. Ethanol is one putative risk factor that has not been evaluated as a mechanism for low blood glucose among sulfonylurea users. We hypothesized that low concentrations of ethanol would reduce blood glucose concentrations in elderly type 2 diabetic patients receiving sulfonylureas during a short-term fast.

RESEARCH DESIGN AND METHODS — A total of 10 type 2 diabetic patients, aged 68 ± 3 years and receiving 20 mg glyburide daily, participated in a prospective double-blind placebo-controlled in-patient study consisting of two 24-h fasts at least 1 week apart. During hours 14 and 15 of the fasting studies, subjects received intravenous infusions of either 4.35 mmol kg^{-1} h^{-1} ethanol (equivalent to one or two alcoholic beverages) or saline placebo in random order. Ethanol, plasma glucose, insulin, and counterregulatory hormones were assessed every 30–60 min during the final 10 h of the fast.

RESULTS — Blood ethanol levels peaked at 17 ± 2 mmol/l (the lower legal limit of intoxication in New Mexico) during the ethanol study. Plasma glucose concentrations did not differ at baseline (placebo 8.5 ± 1.8 vs. ethanol 8.7 ± 1.7 mmol/l; $P = 0.50$), but nadir plasma glucose was lower after the ethanol infusion compared with placebo (4.4 ± 1.2 vs. 5.0 ± 1.4 mmol/l; $P = 0.01$), and the absolute decline in plasma glucose was also greater during the ethanol study than the placebo study (4.7 ± 0.9 vs. 3.6 ± 1.2 mmol/l; $P = 0.01$). Counterregulatory hormone levels were increased during the ethanol study and nonesterified fatty acid concentrations were suppressed compared with the placebo study.

CONCLUSIONS — Low doses of ethanol predispose fasted elderly type 2 diabetic patients to low blood glucose during a short-term fast. This may be one of several mechanisms by which sulfonylurea-induced hypoglycemia occurs in elderly patients.

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Hypoglycemia is the principle adverse event associated with oral sulfonylurea therapy. Retrospective studies have identified advanced age and fasting as the two main risk factors associated with sulfonylurea-induced hypoglycemia (1). Recent data suggest, however, that fasting is well-tolerated in otherwise healthy elderly patients with type 2 diabetes who are taking maximal doses of once-daily sulfonylurea agents (2). Other factors that have been potentially implicated in the development of sulfonylurea-induced hypoglycemia include exercise and ethanol ingestion, but another recent study has demonstrated that moderate exercise is well-tolerated among elderly, fasted patients with type 2 diabetes treated with oral sulfonylurea agents (1,3).

Previous studies have demonstrated that intoxicating levels of blood ethanol (22 mmol/l) after rapid oral administration of ethanol resulted in increased glucose-stimulated insulin secretion and glucose disposal in nondiabetic subjects, but these findings were not observed in patients with type 2 diabetes (4). Nevertheless, given the widely appreciated ability of ethanol to inhibit gluconeogenesis and increase serum insulin concentrations in type 2 diabetes, we hypothesized that low doses of ethanol would reduce ambient glucose concentration in elderly type 2 diabetic patients during a short-term fast when combined with the additional insulinotropic stimulus of a sulfonylurea medication (5).

RESEARCH DESIGN AND METHODS

Study subjects

A total of 10 elderly patients with type 2 diabetes were admitted to the University of New Mexico Clinical Research Center on two occasions for a 24-h fasting study. All study subjects were between 60 and 75 years of age, had a diagnosis of type 2 diabetes for at least 2 years, were treated with sulfonylurea agents (as monotherapy or in combination with metformin) for at least 6 months, and were free of advanced secondary complications of diabetes. Study exclusion criteria included advanced cardiovascular, gastrointestinal, liver, or kidney disease, a BMI >36 kg/m^2, current use of insulin or other medications that interfered with glucose homeostasis (such as glucocorticoids), a history of malignancy or substance abuse, and/or an HbA_{1c} concentration >10%. Subjects were recruited from existing patient databases and from advertisements in the newspaper. All subjects provided written informed consent before

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Abbreviations: ANOVA, analysis of variance; AUC, area under the curve; NEFA, nonesterified fatty acid.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Demographic and descriptive characteristics of the study participants*

Age (years)	67.9 ± 3.3
Sex (M/F)	7/3
Duration of diabetes (years)	7.3 ± 3.7
HbA_{1c} (reference range 4.8–7.8%)	7.8 ± 1.0
BMI (kg/m^2)	31.6 ± 3.7
Baseline sulfonylurea dose (*n*)	
5 mg/day	3
10 mg/day	0
20 mg/day	7

Data are means ± SD or *n*.

the study, as approved by the University of New Mexico Human Research Review Committee. Baseline and descriptive characteristics of the study participants are summarized in Table 1.

Study protocol

All subjects received 20 mg glyburide per day for at least 1 week before each study and on the day of the fast. Three subjects were receiving metformin in doses of 500, 1,500, and 2,500 mg daily upon study enrollment, and these subjects continued to receive metformin throughout the study except on the days of the fasting studies. Subjects were admitted to the University of New Mexico General Clinical Research Center at 1600 on the day before each fasting study, and forearm venous access was established in each arm for the administration of ethanol or placebo (one arm) and for the collection of blood samples (contralateral arm). All subjects subsequently ingested a standard 7 kcal/kg meal according to the recommendations of the American Diabetes Association (50% carbohydrate, 20% protein, 30% fat) at 1800 (6). No further caloric intake was allowed until completion of the 24-h fast at 1800 the following day. The daily dose of glyburide (20 mg) was administered at 0800 on the day of study, and data were collected over the subsequent 10 h (hours 14–24 of the fast). All subjects completed two 24-h fasting studies, during which each of the following treatments were administered in random order during hours 14 and 15 of the fast (0800–1000) in a double-blind study design: *1*) ethanol 4.35 mmol kg^{-1} h^{-1}, or *2*) an equivalent volume of 0.45 mol/l saline (placebo study). The amount of ethanol administered in this study was equivalent to the ethanol content of one to two cans of beer

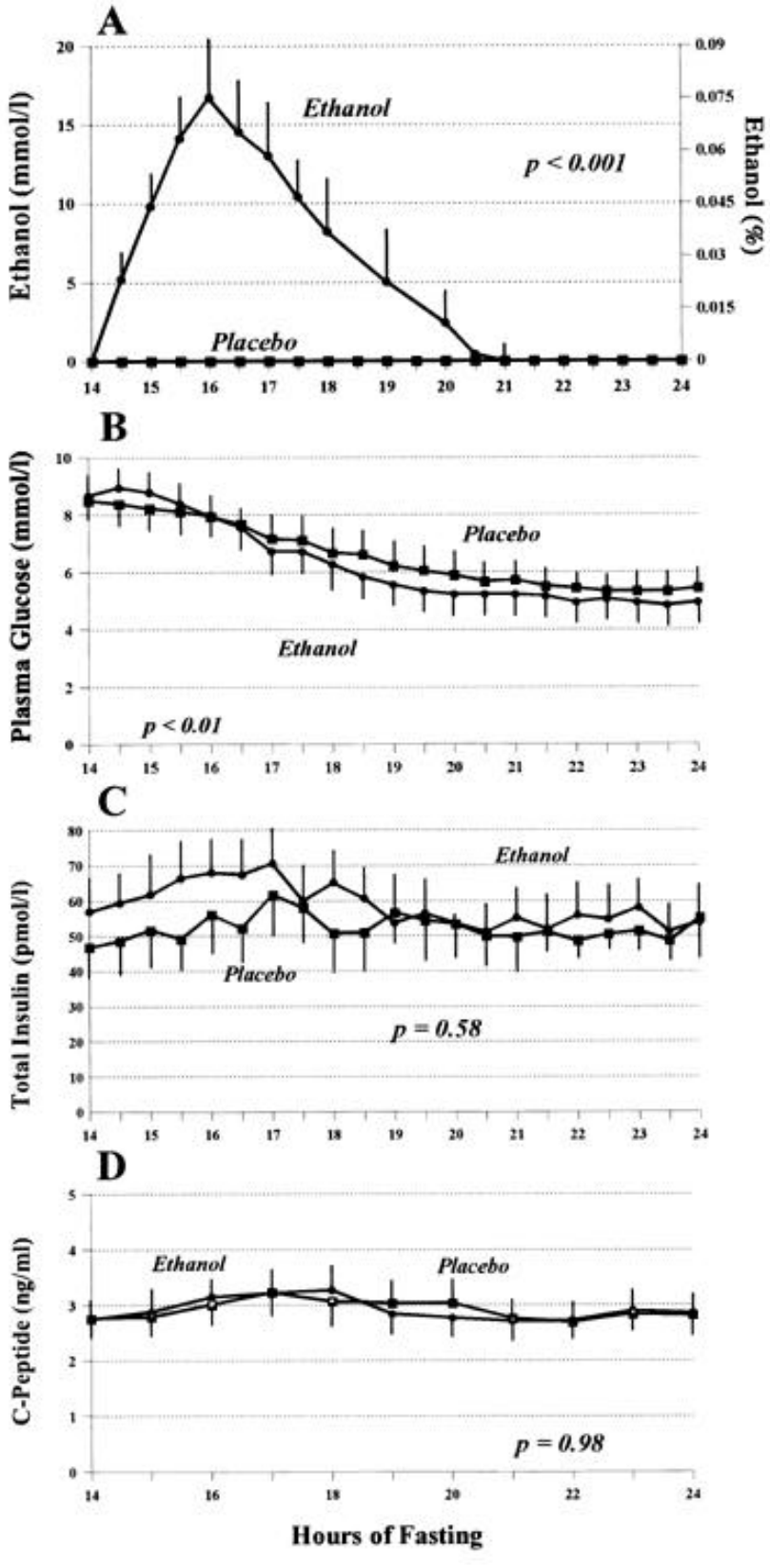

Figure 1—*Concentrations of blood ethanol* (A)*, plasma glucose* (B)*, total insulin* (C)*, and serum C-peptide* (D) *during the final 10 h of a 24-h fast among 10 elderly subjects with type 2 diabetes receiving glyburide 20 mg daily: placebo study,* ■*; ethanol study,* ●*. P values reflect results of the repeated measures analysis of variance.*

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(7). Blood was collected at 0750 and 0800 for baseline determinations, and then every 30 min for the remainder of the 10-h study for determination of plasma glucose, total serum insulin, C-peptide, epinephrine, norepinephrine, and nonesterified fatty acids (NEFAs). Additionally, blood was sampled hourly for determination of glucagon, cortisol, and growth hormone concentrations. All subjects completed a 40-item hypoglycemia symptom questionnaire at baseline and every 2 h during the study, rating symptoms such as fatigue, hunger, nervousness, weakness, tremor, sweating, tachycardia, dyspnea, and difficulty concentrating on a scale of 1 (no symptoms) to 7 (severe symptoms).

Sample analyses

Plasma glucose concentrations were determined with the Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma was separated from blood elements by centrifugation immediately after sampling and frozen at −20°C for later determination, unless capillary blood glucose values were <4.4 mmol/l, at which time plasma glucose levels were determined immediately. Serum insulin concentrations were determined using the Coat-a-Count Insulin radioimmunoassay kit (Diagnostic Products, Los Angeles, CA). C-peptide concentrations were determined using radioimmunoassay (INCSTAR, Steelwater, MN), and NEFA concentrations were determined enzymatically using the Wako Kit (Wako Chemical, Dallas, TX) adapted to the Cobas-Bio (Roche Diagnostic, Somerville, NJ). Samples for plasma epinephrine and norepinephrine were placed on ice immediately after sampling and stored at −70°C until being assayed radioenzymatically (8). Concentrations of cortisol were determined with radioimmunoassay (Coat-a-Count, Diagnostic Products), as were concentrations of growth hormone (Diagnostic Products) and glucagon (Linco Research, St. Louis, MO).

Statistical analysis

All substrate and hormonal variables were compared for an effect of treatment group (placebo vs. ethanol) with a repeated measures analysis of variance and post hoc pairwise comparison, when appropriate, using SAS (SAS Institute, Cary, NC). For the pairwise analyses, data were summarized according to the following summary variables to facilitate interpretation of the observed differences: baseline (mean of 0750 and 0800 samples), peak (maximum value obtained during the 10-h study), nadir (minimum value obtained during the 10-h study), and area under the curve (AUC) calculated according to the trapezoidal rule from baseline.

Table 2—*Results of post hoc analyses for variables with significant differences detected on repeated-measures ANOVA*

Variable	Placebo	Ethanol	*P* value
Plasma glucose (mmol/l)			
Baseline	8.5 ± 1.8	8.7 ± 1.7	0.50
Peak	8.8 ± 1.9	9.1 ± 1.5	0.30
Nadir	5.0 ± 1.4	4.4 ± 1.2	0.01
AUC	−1.8 ± 0.2	−2.3 ± 0.3	0.10
Glucagon (µg/l)			
Baseline	67.8 ± 19.6	65.0 ± 17.3	0.20
Peak	76.1 ± 24.4	96.4 ± 51.7	0.10
Nadir	54.3 ± 14.7	55.3 ± 15.4	0.70
AUC	−1.9 ± 2.6	9.1 ± 16.2	0.04
Plasma epinephrine (pmol/l)			
Baseline	90 ± 83	85 ± 66	0.70
Peak	660 ± 539	1,044 ± 706	0.10
Nadir	58 ± 10	55 ± 0	0.30
AUC	134 ± 133	187 ± 144	0.16
Plasma norepinephrine (µmol/l)			
Baseline	1.7 ± 0.7	1.3 ± 0.5	0.20
Peak	2.7 ± 1.3	3.6 ± 2.6	0.07
Nadir	1.06 ± 0.4	0.9 ± 0.4	0.30
AUC	−0.08 ± 0.4	0.3 ± 0.4	0.02
Serum cortisol (µmol/l)			
Baseline	394 ± 135	281 ± 80	0.001
Peak	475 ± 83	466 ± 121	0.80
Nadir	185 ± 58	152 ± 63	0.10
AUC	−99 ± 97	6 ± 52	0.003
NEFAs (mmol/l)			
Baseline	0.7 ± 0.2	0.7 ± 0.26	0.50
Peak	1.2 ± 0.4	1.4 ± 0.6	0.50
Nadir	0.6 ± 0.2	0.2 ± 0.1	0.0001
AUC	0.07 ± 0.1	−0.07 ± 1.7	0.008

Data are means ± SD or *P* value.

RESULTS — Ethanol concentrations peaked after 2 h of intravenous ethanol infusion at 17 ± 2 mmol/l (0.08 ± 0.01%, the legal limit of intoxication in New Mexico) during the ethanol study, while levels were undetectable during the placebo study (Fig. 1*A*).

Repeated measures analysis of variance demonstrated a significant difference between the treatment groups in plasma glucose concentrations (Fig. 1*B*), and post hoc testing revealed that the absolute decline in plasma glucose was greater during the ethanol study compared with the placebo study (4.7 ± 0.9 vs. 3.6 ± 1.3 mmol/l; $P = 0.01$), as was the rate of decline of plasma glucose (−0.0077 ± 0.002 vs. −0.005 ± 0.002 µmol/l per min; $P = 0.01$) (Table 2). There was no demonstrable difference between the two study groups in baseline or peak plasma glucose, but nadir plasma glucose was significantly decreased after the ethanol study compared with placebo (4.3 ± 1.2 vs. 5.0 ± 1.4 mmol/l; $P = 0.01$). One subject experienced frank hypoglycemia (defined as plasma glucose <2.8 mmol/l with typical hypoglycemic symptoms or any plasma glucose level <2.2 mmol/l) during both arms of the study. In this subject, the hypoglycemia occurred after 5 h in the ethanol study and after 8.5 h in the placebo study.

Serum concentrations of insulin and C-peptide did not differ between the two study conditions, as shown in Fig. 1*C* and *D*, respectively.

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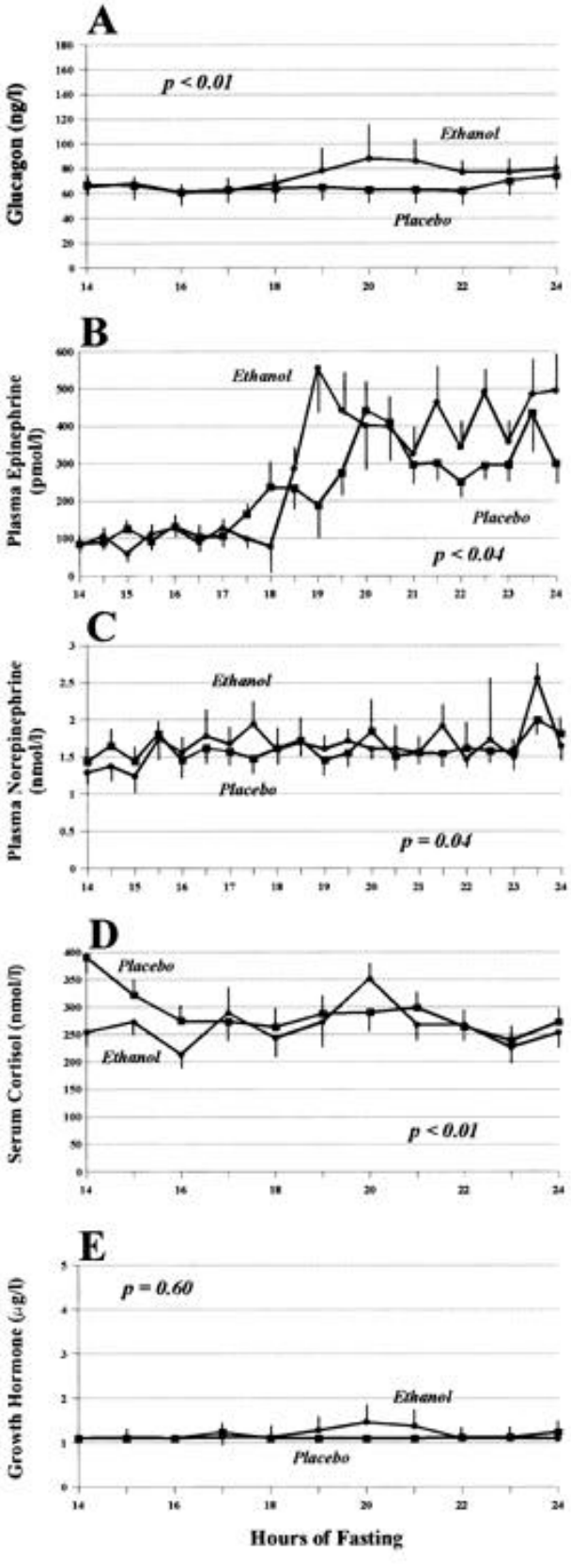

Figure 2—*Concentrations of plasma glucagon* (A)*, plasma epinephrine* (B)*, plasma norepinephrine (C), serum cortisol* (D)*, and serum growth hormone* (E) *during the final 10 h of a 24-h fast among 10 elderly subjects with type 2 diabetes receiving glyburide 20 mg daily. Legend and* P *values the same as in Fig. 1.*

Counterregulatory hormones

Plasma glucagon concentrations were significantly different between the two study conditions by repeated measures analysis of variance (ANOVA) (P = 0.009), and post hoc testing confirmed that glucagon AUC concentrations were increased in the ethanol study compared with the placebo study (P = 0.04, Fig. 2*A*, Table 2). There were no differences between the study groups with respect to baseline, peak, or nadir concentrations of glucagon.

Repeated measures ANOVA demonstrated a statistically significant difference in plasma epinephrine concentrations during the ethanol study compared with the placebo study (P = 0.04, Fig. 2*B*). Post hoc testing, however, failed to reveal statistically significant differences in any of the four summary variables examined, suggesting that the differences between the study conditions were principally related to the time course of epinephrine concentrations (e.g., slope) rather than to epinephrine levels per se (Table 2). Similarly, repeated measures ANOVA demonstrated a statistically significant difference in norepinephrine response between the study conditions (P = 0.04), and post hoc testing showed that norepinephrine AUC concentrations were increased in the ethanol study compared with the placebo study (P = 0.02, Table 2).

As shown in Fig. 2*C*, serum cortisol concentrations remained low throughout both studies, but serum cortisol concentrations were significantly different between the two study conditions by repeated measures ANOVA ($P < 0.01$). Specifically, post hoc testing revealed that baseline cortisol concentrations were reduced in the ethanol study compared with the placebo study, while baseline-adjusted cortisol AUC concentrations were increased in the ethanol study compared with the placebo study (Table 2).

Serum growth hormone concentrations were below the limits of assay detection (<1 μg/l) in the majority of subjects under both study conditions, and no statistically significant differences were observed in growth hormone concentrations (P = 0.60, Fig. 2*D*).

NEFAs

Concentrations of NEFA were reduced during the ethanol study compared with the placebo study ($P < 0.001$, Fig. 3). As shown in Table 2, post hoc analysis revealed that both nadir NEFA (P =

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0.0001) and NEFA AUC concentrations were reduced in the ethanol group compared with the placebo group ($P = 0.008$).

Hypoglycemia questionnaire

There were no statistically significant differences between the treatment groups with respect to responses to the hypoglycemia questionnaire in this study (data not shown).

CONCLUSIONS — Ethanol is the most widely used recreational drug in western industrialized countries. The 1988 U.S. National Health Interview Survey demonstrated that 68% of men and 47% of women in the U.S. regularly drink alcohol in varying degrees between light and heavy consumption (9). This fact may have relevance to the observation that the risk of serious hypoglycemia is ~2 per 100 person-years among elderly people treated with sulfonylurea agents (10). As such, the role of ethanol in the pathogenesis of sulfonylurea-induced hypoglycemia needs to be investigated. Although there is a large body of medical literature examining the effect of alcohol on carbohydrate metabolism in healthy, nondiabetic individuals, there are only limited data on the effects of ethanol in patients with type 2 diabetes. Studies involving nondiabetic individuals, for example, have shown that elderly nondiabetic subjects exhibit a deterioration in glucose tolerance after ethanol administration compared with younger men (11,12). Conversely, in individuals with diet-treated type 2 diabetes, Christiansen et al. (13) have shown that the ability of ethanol to induce hypoglycemia is attenuated because there is no apparent increase in insulin sensitivity in response to ethanol administration during hyperinsulinemic-euglycemic clamp experiments. Finally, Clore et al. (14) have demonstrated that ethanol infusion does not alter glucose AUC concentrations in obese subjects with type 2 diabetes after a 3-day fast compared with saline control studies. In none of these studies, however, were subjects exposed to the endogenous hyperinsulinemia produced by maximal doses of sulfonylurea medications.

We have recently demonstrated that contrary to retrospective study data, fasting is well-tolerated in otherwise healthy elderly patients with type 2 diabetes who are taking maximal doses of once-daily sulfonylurea agents (2). The current study demonstrates that low doses of ethanol may predispose elderly type 2 diabetic patients to sulfonylurea-induced low blood glucose during a short-term fast. The amount of ethanol infused in this study was equivalent to ~1 ounce of ethanol (or 1 alcoholic beverage) over the course of 2 h, an amount commonly ingested on a regular basis by many patients with type 2 diabetes. These results suggest that minimal or moderate ethanol ingestion may contribute to the development of sulfonylurea-induced hypoglycemia in type 2 diabetic patients. Koivisto et al. (15) have reported that patients with type 2 diabetes exhibit increased insulin concentrations but exhibit no change in plasma glucose after ingesting a meal in combination with 1 g/kg ethanol, as compared with eating a meal without ethanol. Despite the fact that the amount of ethanol administered in this study was three to four times the dose used in the present study, blood ethanol levels were only slightly higher than those we observed (24.5 mmol/l or 0.11%), demonstrating the significant first-pass metabolism of ethanol that occurs when it is ingested orally. Nevertheless, according to the data presented here, ethanol-induced reductions in plasma glucose observed during fasting are not attributable to increased endogenous insulin secretion. Moreover, the observed increase in glucagon that occurred during ethanol infusion in this study can be explained by the reduced plasma glucose concentrations observed in this arm of the study, and the small increase in cortisol concentrations that occurred during ethanol infusion is unlikely to be clinically significant.

The observed decrease in NEFA concentrations in this study is important because of the well-documented role of NEFAs in glucose homeostasis among subjects with type 2 diabetes. Specifically, NEFAs are associated with inhibition of insulin-stimulated glucose utilization and hepatic insulin resistance (16). The reduction in NEFA concentrations observed with ethanol is probably mediated through a suppression of lipolysis secondary to the accumulation of acetate and/or lactate (17,18). There is additional evidence to suggest that ethanol is a preferred fuel by many body tissues, resulting in decreased oxidation of both fat and carbohydrate stores (11). Interestingly, Avogaro et al. (19) have demonstrated that alcohol-induced suppression of NEFAs prevents the normal lipolytic response to catecholamines during hypoglycemia and, further, that ethanol-induced reductions in plasma glucose are attenuated by the intravenous administration of sufficient Intralipid to maintain NEFA concentrations. Providing further support for the importance of NEFAs in glucose homeostasis during ethanol administration, Fanelli et al. (20) have shown that increases in hepatic glucose production that occur as a result of counterregulatory hormone release in nondiabetic subjects during insulin-induced hypoglycemia can be markedly attenuated by the addition of acipimox, a fatty acid oxidase inhibitor, which prevents the normal rise in NEFAs that occurs during recovery from hypoglycemia (20). Taken together, these studies suggest that fatty acids play a critical role in glucose homeostasis during ethanol ingestion. Our study suggests that these mechanisms are operative after the relatively mild reductions in plasma glu-

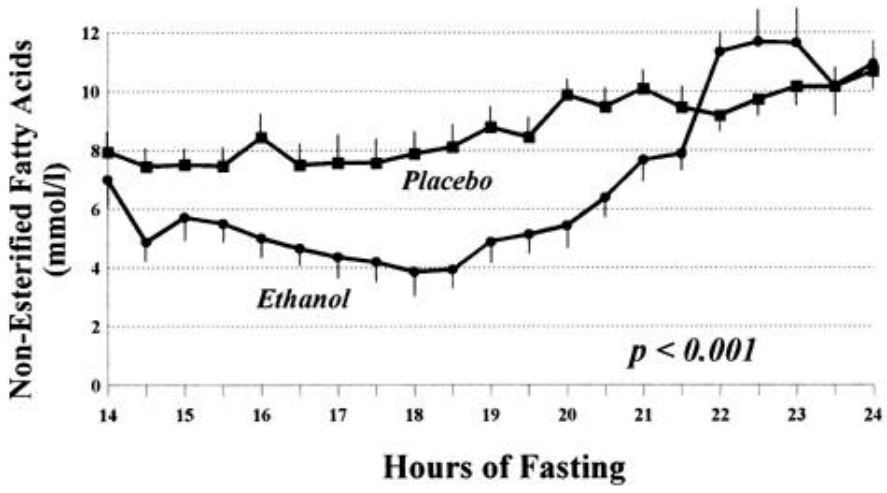

Figure 3—*Concentrations of NEFAs during the final 10 h of a 24-h fast among 10 elderly subjects with type 2 diabetes receiving glyburide 20 mg daily. Legend and* P *values the same as in Fig. 1.*

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cose precipitated by low-dose ethanol in patients with type 2 diabetes.

Many potential cardiovascular benefits have been attributed to moderate chronic ethanol consumption in nondiabetic individuals, including increased HDL cholesterol concentrations and reduced fibrinogen and platelet aggregation, but these benefits have not been definitively extended to patients with type 2 diabetes. In fact, various studies have documented decreased fibrinogen levels due to ethanol in nondiabetic subjects, increased fibrinogen levels attributable to diabetes and increased triglycerides, unchanged HDL cholesterol concentrations, and unchanged insulin sensitivity among type 2 diabetic patients consuming moderate amounts of ethanol (13,21,22). One recent epidemiological study, however, has demonstrated an impressive decrease in the risk of cardiovascular death and over-all mortality associated with increasing alcohol intake among patients with older-onset diabetes, suggesting that the beneficial cardiovascular effects of ethanol can be extended to such patients and that the cardiovascular benefits of ethanol in diabetes may even exceed those observed in nondiabetic subjects (23). The putative beneficial effects of ethanol have not, however, been extended to acute ethanol administration and so may not apply to the current study.

We chose to use intravenous ethanol in this study to minimize the variability in gastrointestinal absorption of ethanol that occurs with oral administration and to assure that target levels for blood alcohol were achieved. It is conceivable, however, that orally ingested ethanol has direct effects on hepatic glucose production, which may exacerbate or attenuate the tendency to hypoglycemia that we observed. Classically, ethanol is believed to cause hypoglycemia by inhibiting hepatic gluconeogenesis due to the consumption of NAD^+ during its metabolism, but Puhakainen et al. (24) have demonstrated that the inhibition of gluconeogenesis by ethanol does not decrease total hepatic glucose output in patients with type 2 diabetes, suggesting the existence of a regulatory mechanism in the liver that maintains total glucose output (24). Secondly, the failure of this study to demonstrate an increased rate of occurrence of frank, symptomatic hypoglycemia after ethanol administration may reflect the fact that a fast of 24-h duration is insufficient to observe such a difference or that ethanol levels were insufficient to precipitate frank hypoglycemia in this study. Finally, the plasma glucose response to high doses of glyburide is quite variable, and the use of a maximum dose of glyburide may be excessive and may unnecessarily increase the risk for hypoglycemia in patients who are able to achieve target glucose goals on lower doses of glyburide (25,26).

We conclude that low doses of ethanol predispose elderly, sulfonylurea-treated patients with type 2 diabetes to low blood glucose concentrations. Combined with other factors known to reduce plasma glucose concentration, alcohol may significantly contribute to the development of hypoglycemia in susceptible individuals with diabetes.

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References

1. Seltzer HS: Drug-induced hypoglycemia: a review of 1418 cases. *Endocrinol Metab Clin North Am* 18:163–183, 1989
2. Burge MR, Schmitz-Fiorentino K, Fischette C, Qualls CR, Schade DS: A prospective trial of risk factors for sulfonylurea-induced hypoglycemia in type 2 diabetes mellitus. *JAMA* 279:137–143, 1998
3. Riddle MC, McDaniel PA, Tival LA: Glipizide–GITS does not increase the hypoglycemic effect of mild exercise during fasting in NIDDM. *Diabetes Care* 20:992–994, 1997
4. Nikkila EA, Taskinen MR: Ethanol-induced alterations of glucose tolerance, postglucose hypoglycemia, and insulin secretion in normal, obese and diabetic subjects. *Diabetes* 24:933–943, 1975
5. Christiansen C, Thomsen C, Rasmussen O, Glerup H, Berthelsen J, Hansen C, Orskov H, Hermansen K: Acute effects of graded alcohol intake on glucose, insulin, and free fatty acid levels in non-insulin-dependent diabetic subjects. *Eur J Clin Nutr* 47:648–652, 1993
6. American Diabetes Association: Nutrition recommendations and principles for people with diabetes mellitus. *Diabetes Care* 20 (Suppl. 1):S14–S17, 1997
7. Zeman FJ: Nutritional care in specific clinical disorders. In *Clinical Nutrition and Dietetics*. New York, Macmillan, 1983, p. 517–553
8. Shah SD, Clutter WE, Cryer PE: External and internal standards in the single isotope derivative (radioenzymatic) assay of plasma norepinephrine and epinephrine in normal humans and persons with diabetes mellitus or chronic renal failure. *J Lab Clin Med* 106:624–629, 1985
9. Kranzler HR, Babor TF, Moore P: Alcohol use disorders. In *Psychiatry*. 1st ed. Tasman A, Kay J, Lieberman JA, Eds. Philadelphia, WB Saunders, 1997, p. 755–778
10. Shorr RI, Ray RA, Daugherty JR, Griffin MR: Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med* 157:1681–1686, 1997
11. Shelmet JJ, Richard GA, Skutches CL, Hoeldtke RD, Owen OE, Boden G: Ethanol causes acute inhibition of carbohydrate, fat and protein oxidation and insulin resistance. *J Clin Invest* 81:1137–1145, 1988
12. Boden G, Chen X, Desantis R, White J, Mozzoli M: Effects of ethanol on carbohydrate metabolism in the elderly. *Diabetes* 42:28–34, 1993
13. Christiansen C, Thomasen C, Rasmussen O, Hansen C, Hermansen K: The acute impact of ethanol on glucose, insulin, triacylglycerol, and free fatty acid responses and insulin sensitivity in type 2 diabetes. *Br J Nutr* 76:669–675, 1996
14. Clore JN, Blackard WG: Suppression of gluconeogenesis after a 3-day fast does not deplete liver glycogen in patients with NIDDM. *Diabetes* 43:256–262, 1994
15. Koivisto VA, Tulokas S, Toivonen M, Happa E, Pelkonen R: Alcohol with a meal has no adverse effects on postprandial glucose homeostasis in diabetic patients. *Diabetes Care* 16:1612–1614, 1993
16. Randle PJ, Kerbey AL, Espinal J: Mechanisms decreasing glucose oxidation in diabetes and starvation: role of lipid fuels and hormones. *Diabetes Metab Rev* 4:623–638, 1988
17. Lieber CS, Leevy CM, Stein SW, George WS, Cherrick GR, Abelmann WH, Davidson CS: Effect of ethanol on plasma free fatty acids in man. *J Lab Clin Med* 59:826–832, 1962
18. Bjorntrop P: The effect of lactic acid on adipose tissue metabolism in vitro. *Acta Med Scand* 178:253–255, 1965
19. Avogaro A, Beltramello P, Gnudi L, Maran A, Valerio A, Miola M, Marin N, Crepaldi C, Confortin L, Costa F: Alcohol intake impairs glucose counterregulation during acute insulin-induced hypoglycemia in IDDM patients: evidence for a critical role of free fatty acids. *Diabetes* 42:1626–1634, 1993
20. Fanelli C, Calderone S, Epiffano L, De Vincenzo A, Modarelli F, Pampanelli S, Perriello G, De Feo P, Brunetti P, Gerich JE: Demonstration of a critical role for free fatty acids in mediating counterregulatory stimulation of gluconeogenesis and suppression of glucose utilization in humans. *J Clin Invest* 92:1617–1622, 1993
21. Folsom AR, Qamhieh HT, Flack JM, Hilner

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JE, Liu K, Howard BV, Tracy RP: Plasma fibrinogen: levels and correlates in young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Epidemiol* 138:1023–1036, 1993
22. Ben G, Gnudi L, Maran A, Gigante A, Duner E, Iori E, Tiengo A, Avogaro A: Effects of chronic alcohol intake on carbohydrate and lipid metabolism in type 2 (non-insulin-dependent) diabetes. *Am J Med* 90:70–76, 1991
23. Valmadrid CT, Klein R, Moss SE, Klein BEK, Cruickshanks KJ: Alcohol intake and the risk of coronary heart disease mortality in persons with older-onset diabetes mellitus. *JAMA* 282:239–246, 1999
24. Puhakainen I, Koivisto VA, Yki-Jarvinen H: No reduction in total hepatic glucose output by inhibition of gluconeogenesis with ethanol in NIDDM patients. *Diabetes* 40:1319–1327, 1991
25. Jaber LA, Antal EJ, Welshman IR: Pharmacokinetics and pharmacodynamics of glyburide in young and elderly patients with non-insulin-dependent diabetes mellitus. *Ann Pharmacother* 30:472–475, 1996
26. Melander A, Donnelly R, Rydberg T: Is there a concentration-effect relationship for sulphonylureas? *Clin Pharmacokinet* 34: 181–188, 1998

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