DISCUSSION

Our data indicate that the fructosamine level may be more effective than the HbA_{1c} level in detecting changes in glycemic control over a short period of observation. This study agrees with the finding of others demonstrating that the fructosamine level is a valid index of short-term glycemic control (6–8). However, the data also indicated a steady and consistent drop in the HbA_{1c} at each week of study, not reaching a significant fall until 3 wk of study. This observation suggests that the HbA_{1c} may reflect changes in glycemic control more rapidly than has been traditionally appreciated. This rapid drop in fructosamine activity as a parameter of glucose control may be explained by the following observations. The fructosamine assay measures total glycosylated serum protein (4,5), and measurement of serum fructosamine has been largely shown to correlate well with the glycosylated albumin level (4). As glycosylated albumin levels fall due to the shorter half-life of the albumin component of the serum proteins measured, a fall in serum fructosamine levels as was confirmed by our study would be possible. A second reason that the fructosamine level dropped more rapidly over the time of the study may relate to an altered half-life of the glycosylated albumin itself. Previously performed studies have suggested a more rapid clearance of glycosylated albumin compared with native albumin, and this may relate clinically to a more rapid reduction in serum glycosylated protein levels (9,10).

In summary, we have shown that the fructosamine level may be more sensitive than the HbA_{1c} level in detecting mean blood glucose changes over a short period of observation (~2–3 wk). Fructosamine appears to be as effective as HbA_{1c} in its ability to correlate with mean blood glucose in this cross-sectional study in both type I and type II diabetic patients. However, due to the increased sensitivity of the fructosamine in detecting glycemic changes, caution must be taken in interpreting glycemic control from infrequent use of this assay, because it may not provide a reliable overview of glycemic control over a period such as 2–4 mo as has been firmly established with HbA_{1c}.

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Ineffectiveness of SMS 201-995 in Severe Hyperinsulinemia

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The long-acting somatostatin analogue SMS 201-995 has been used with impressive success in the treatment of certain endocrine disorders, including acromegaly (1–4), the Verner-Morrison syndrome (5,6), and the carcinoid syndrome (7,8). There is less information with respect to the effectiveness of this drug in the treatment of organic hyperinsulinism (β-cell adenomas, carcinomas, hyperplasia, and nesidioblastosis). We report two cases with severe hyperinsulinism caused by islet cell adenomas. In both cases, protracted hypoglycemia and hyperinsulinemia were not improved by SMS 201-995.

CASE REPORTS

Patient 1. A 63-yr-old obese Caucasian woman (wt 240 lb, ht 5'6") was admitted to the General Clinical Research Center at Temple University Hospital with a 6-mo history of episodes of sweating, dizziness, slurred speech, and inability to read. At first, these episodes occurred only late at night and could be relieved by eating. Later, they became more frequent and difficult to alleviate. Several blood samples, taken after an overnight fast, showed glucose concentrations between 20 and 40 mg/dl and insulin concentrations between 80 and 400 μU/ml. Transhepatic portal venous blood sampling with measurements of insulin localized the origin of the excessive insulin secretion between the midsection and the tail of the pancreas. On laparotomy, a 17 × 15-mm well-encapsulated tumor was found and enucleated from the midsection of the body of the pancreas. Immunohistochemistry and electron microscopy demonstrated that the tumor cells predominantly contained insulin. Postoperatively, serum glucose and insulin concentrations remained normal without therapy.

Patient 2. A 69-yr-old obese Caucasian woman (wt 236 lb; ht 4'11") was admitted to the General Clinical Research Center of Temple University Hospital in November 1984 with a history of several hypoglycemic attacks. Her serum glucose and insulin concentrations after an overnight fast ranged from 20 to 60 mg/dl and from 61 to 160 μU/ml, respectively. Her plasma C-peptide concentration was 11 ng/ml (normal 0.9–4.0 ng/ml). No sulfonylurea or sulfonylurea metabolites were detected in her urine, excluding the possibility of surreptitious intake of these drugs. Plasma follicle-stimulating hormone, prolactin, human growth hormone, and cortisone concentrations were normal. Selective splenic and inferior gastroduodenal arteriography and abdominal computed tomography scans were negative. No tumor was found on exploratory laparotomy, and a 70% distal pancreatectomy was performed. Postoperatively, the patient remained asymptomatic without treatment for ~1.5 yr; then she began to experience hypoglycemic attacks of progressively increasing frequency and severity. Her weight increased to 320 lb. After admission to the hospital in June 1987, it was difficult to keep her plasma glucose concentration >50 mg/dl despite frequent feedings (every 1–2 h). Complete resection of the remaining pancreas revealed a small adenoma (0.5 × 0.3 cm). Postoperatively, her plasma glucose rose to >500 mg/dl, and the patient was started on treatment with insulin.

SPECIAL STUDIES

Blood samples were collected from both patients through indwelling venous catheters every 1 or 2 h during the day and several times during the night for determination of plasma glucose (Beckman glucose analyzer; Fullerton, CA). Serum insulin and plasma glucagon were measured by radioimmunoassay in samples always taken before meals, snacks, or intravenous glucose infusions (9,10).

Patient 1. Before the start of treatment with SMS 201-995, most of the patient's plasma glucose concentrations ranged between 40 and 50 mg/dl despite frequent meals, and her serum insulin concentrations fluctuated between 20 and 400 μU/ml (Fig. 1). SMS 201-995 (50 μg s.c. twice daily) did not increase glucose nor decrease insulin concentrations. On the contrary, insulin peaks were higher during than before SMS 201-995 treatment. Diazoxide (200 mg orally twice daily) given 1 day after discontinuation of SMS 201-995 resulted in prompt normalization of plasma glucose concentrations. Unfortunately, insulin measurements were not performed.

Patient 2. Before the start of treatment with SMS 201-995, plasma glucose concentrations were consistently low (mean ± SD, 56 ± 14 and 57 ± 12 mg/dl on days 1 and 2, respectively) despite food intake every 1 or 2 h (Table 1; Fig. 2). Serum insulin concentrations fluctuated widely between 125 and 1250 μU/ml. SMS 201-995 (50 and 100 μg s.c. twice daily) did not raise plasma glucose but instead was followed on several occasions by severe hypoglycemia. Mean insulin concentration was unchanged from the pretreatment period during the 1st day of SMS 201-995 treatment and was slightly lower (466 ± 292 μU/ml) during the 2nd day.

Diazoxide was given for 2 days (200 mg on day 1 and 400 mg on day 2); afterward, it had to be discontinued because of uncontrollable fluid retention. Diazoxide also had no effect on glucose concentrations. It appeared to have some lowering effect on insulin

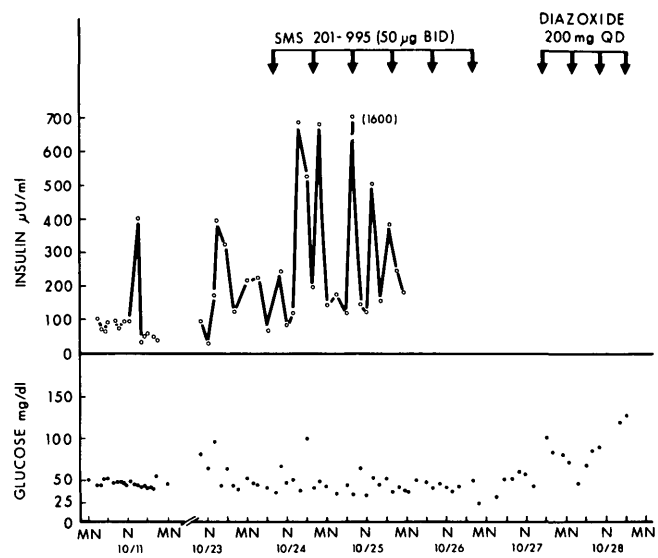

FIG. 1. Effects of SMS 201-995 and of diazoxide on plasma glucose and insulin concentrations in patient with insulinoma. MN, midnight; N, noon. *Arrows* indicate injections of SMS 201-995 or diazoxide. BID, twice a day.

TABLE 1
Effect of SMS 201-995 on mean daily glucose, insulin, and glucagon concentrations in patient 2

	Glucose (mg/dl)	Insulin (μU/ml)	Glucagon (pg/ml)
No treatment			
6/23–24 (24 h)	56 ± 14 (14)	595 ± 277 (12)	
6/24–25 (24 h)	57 ± 12 (14)	689 ± 327 (15)	163 ± 42 (10)
SMS 201-995			
6/25–26 (24 h)	57 ± 23 (14)	619 ± 314 (13)	
6/26–27 (18 h)	53 ± 30 (14)	466 ± 292 (9)	71 ± 35 (9)
Diazoxide			
6/28–29 (24 h)	53 ± 8 (11)	614 ± 291 (11)	
6/29–30 (24 h)	58 ± 13 (12)	450 ± 215 (11)	160 ± 144 (11)

Values are means ± SD of 24-h periods on specified dates (except for 6/26 when blood was collected for 18 h only). Number of samples tested is indicated in parentheses.

concentrations, which, however, remained grossly elevated.

DISCUSSION

Somatostatin failed to raise blood glucose concentrations in both patients. The apparent reason was its inability to significantly lower the very high insulin levels. In patient 1, insulin peaks appeared to be even higher during than before SMS 201-995 treatment (Fig. 1). In patient 2, there was a small (27%) decrease in the mean 24-h insulin concentration on day 2 of treatment. Insulin concentrations, however, remained grossly elevated (ranging from 150 to >1000 μU/ml) for most of the day. At these concentrations, insulin completely suppresses hepatic glucose production (11) and maximally stimulates peripheral glucose utilization (12). The cause for the apparent ineffectiveness of the long-acting somatostatin analogue is not entirely clear. It cannot be excluded that higher doses and/or more frequent injections would have been more effective. The drug was given in doses of 50 μg twice daily in patient 1 and 100 μg twice daily in patient 2. These dosages have been demonstrated to effectively suppress other polypeptide hormones and to profoundly affect symptomatology in patients with vipomas, acromegaly, and carcinoid syndrome (1–8). In patient 2, we also infused SMS 201-995 intravenously (100 μg/h) to exclude the possibility that subcutaneous administration prevented attainment of sufficiently high blood concentrations. However, plasma glucose fell from 75 to 28 mg/dl during the 1st h of infusion, and the experiment had to be discontinued. On the other hand, it has been shown that SMS 201-995 suppressed insulin release only briefly in normal subjects (13) and in patients with acromegaly (3,4) and that some insulinomas were resistant to somatostatin (14). These observations may provide an explanation for its failure to achieve clinical improvement in our patients, who had extremely high rates of insulin release.

In patient 2, SMS 201-995 actually aggravated the patient's hypoglycemia. The patient frequently became symptomatic ~1 h after SMS 201-995 and needed oral and/or intravenous dextrose. This caused wide fluctuations in her blood glucose concentrations (Fig. 2) and more than doubled the standard deviation of her mean 24-h glucose values (Table 1). It may be relevant that we have noticed several episodes of hypoglycemia in diabetic patients who received their usual dosage of insulin together with SMS 201-995 for therapy of orthostatic hypotension (15) and that Ipp et al. (16) have recently shown that somatostatin impairs the clearance of insulin. In addition, others have successfully used this drug to lower postprandial hyperglycemia in patients with diabetes (17,18). Potent and prolonged suppression of release of glucagon and growth hormone and inhibition of nutrient absorption from the gut may contribute to the tendency of SMS 201-995 to cause hypoglycemia in some patients (19,20). Our observation that SMS 201-995 suppressed plasma glucagon concentrations in patient 2 supported this hypothesis.

So far, there have been only a few reports of insulin-

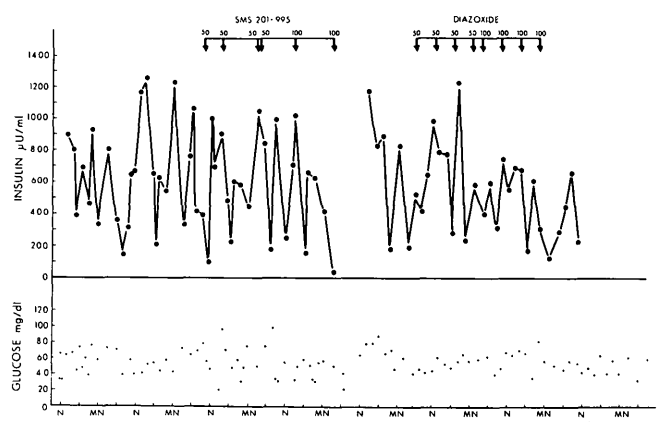

FIG. 2. Effects of SMS 201-995 and of diazoxide on plasma glucose and insulin concentrations in patient with insulinoma.

omas treated with SMS 201-995. Osei et al. (21) reported a 50–70% decrease in serum insulin and a 200-mg/dl increase in blood glucose concentration in a patient with malignant insulinoma treated with SMS 201-995 (50 μg s.c. twice daily; 21). Inasmuch as this patient was given diazoxide (600 mg/day) together with SMS 201-995, it is difficult to be certain that the observed improvements were caused by the somatostatin analogue alone. Verschoor et al. (22) have treated three patients with benign β-cell adenoma with SMS 201-995 in dosages ranging from 100 to 300 μg/day. In two patients, they observed a >50% decrease in plasma insulin and a concomitant increase in glucose to hyperglycemic levels. In the third patient, the drug was ineffective. Kvols et al. (23) reported the use of SMS 201-995 in four patients with insulinoma. The drug normalized glucose concentrations in one patient, had some beneficial effects in two patients, but was ineffective in the fourth patient. Data from the literature, including our own, suggested that SMS 201-995 given in regular dosages (50–300 μg/day) raised blood glucose levels in most patients with moderately elevated insulin concentrations (<50 μU/ml) (21–24). On the other hand, patients with very high insulin levels (>100 μU/ml) either needed much larger dosages of the drug (≤1500 μg/day) for very long periods, were unresponsive, or became worse with treatment.

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