Brief Notes and Comments

Effect of Intravenous Tolbutamide on Serum Insulin Levels in Pancreatic Diabetes

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SUMMARY

Intravenous tolbutamide was administered to seven patients with diabetes secondary to chronic calcific pancreatitis who had not previously received insulin. A matched group of normal controls was similarly investigated. The pancreatic diabetic patients were found to respond to tolbutamide with a significantly impaired serum insulin rise compared to the control group, while their fall in plasma glucose was delayed and significantly less pronounced. The relationship between insulin responses in pancreatic and in primary diabetes is briefly discussed and therapeutic implications of the findings are considered. DIABETES *18*:499-501, July, 1969.

Chronic pancreatitis is often complicated by the development of diabetes.[1,2] Recent investigations with the use of insulin radioimmunoassay have shown that insulin responses after glucose[3,4] and intensive beta cell stimulation[5] are diminished in this situation. In the present study the effect of intravenous tolbutamide alone on the pancreatic insulin secreting capacity of patients with diabetes secondary to chronic pancreatitis has been examined in an attempt to elucidate further the pathogenesis of the syndrome and because of possible therapeutic implications.

MATERIAL AND METHODS

The subjects of the study were seven lean patients with unequivocal clinical and investigative features of chronic pancreatitis; all had radiological evidence of pancreatic calcification. Alcohol was believed to be related to the etiological factor. Despite this, hepatic disease was not detected clinically, biochemically or histologically in any patient. The presence of diabetes had previously been confirmed on the basis of a diabetic oral glucose tolerance test.[6] Pertinent characteristics of these patients are given in table 1. No patient had previously received insulin, although five were taking chlorpropamide; none was ketotic. Familial diabetes was excluded as far as possible by a careful systematic inquiry.

TABLE 1

Characteristics of patients studied

Patient	Age	Sex	Weight (per cent of ideal)	Fasting plasma glucose* (mg. per 100 ml.)	Therapy
A.F.	51	M	94	281	chlorpropamide
R.P.	53	F	100	195	chlorpropamide
P.B.	51	M	97	97	diet
M.O.	67	M	80	292	chlorpropamide
J.D.	42	M	100	159	chlorpropamide
M.C.	42	M	91	110	none
M.S.	59	M	96	121	chlorpropamide
Mean	52		94	179	

*Value during present test

Seven active, healthy, nonobese volunteers (six males, one female), belonging to a similar age group served as normal controls. None had a family history of diabetes, and their glucose tolerance tests were normal.

All subjects received an adequate carbohydrate intake prior to testing, and in those taking chlorpropamide the drug was stopped for four days before the test. It was felt that with a half-life of thirty-five hours, drug activity would be slight at the time of testing. After an overnight fast, each subject received an intravenous injection of 1 gm. tolbutamide over three minutes. Venous blood was obtained via an indwelling cannula placed in an antecubital vein. Samples for plasma and serum were taken at fasting and at 5, 10, 20, 30, 60 and 90 minutes after the end of the injection. They were separated and stored at —20° C. until analyses were made.

Plasma glucose was determined by the ferricyanide method of Hoffman[7] modified for the AutoAnalyzer. Serum immunoreactive insulin (IRI) was assayed by the radioimmunoassay procedures of Hales and Randle,[8] as modified by the Radiochemical Centre, Amersham Data Sheet 5616.

RESULTS

Serum insulin (IRI) response (figure 1)

There was no significant difference between the fasting IRI levels of the two groups ($p < 0.5$). In the normal subjects,

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the mean IRI level rose promptly to a peak of 113 μU./ml. after five minutes, with subsequent gradual decline to the fasting level at 90 min. On the other hand, in the pancreatic diabetic patients the IRI response to tolbutamide was small, with a peak of only 28 μU./ml. at five minutes. The differences between the normal and pancreatitis groups were statistically significant at 5, 10 and 20 minutes ($p < 0.005$, $p < 0.01$, $p < 0.02$ respectively).

Plasma glucose response (table 1 and figure 1)

In the patients with pancreatitis the mean ± S.E.M. fasting plasma glucose value (179 ± 30 mg. per 100 ml.) was almost double the corresponding value (91 ± 4 mg. per 100 ml.) for the normal controls ($p < 0.02$). The normal subjects had a sharp decline in plasma glucose with a maximum fall of 43 per cent of the mean fasting value at thirty minutes. In the pancreatic diabetics, the fall in glucose was delayed and significantly less pronounced ($p < 0.001$ at 10, 20 and 30 minutes and $p < 0.05$ at sixty minutes). When the area under the curve was related to the mean increment in insulin area during the tolerance test however, the ratio obtained (0.9) was similar to that in the normal subjects (1.0). This suggests that the diminished glucose fall in the patients with pancreatitis simply reflected deficient insulin secretion (and not endogenous insulin resistance).

DISCUSSION

The findings in the present study further support the thesis of impaired insulin reserve in patients who develop diabetes secondary to chronic pancreatitis. Tolbutamide, a known insulinogenic stimulus, caused only slight increments in serum IRI in these subjects when compared to normal controls. Associated with this, the fall in blood glucose was diminished.

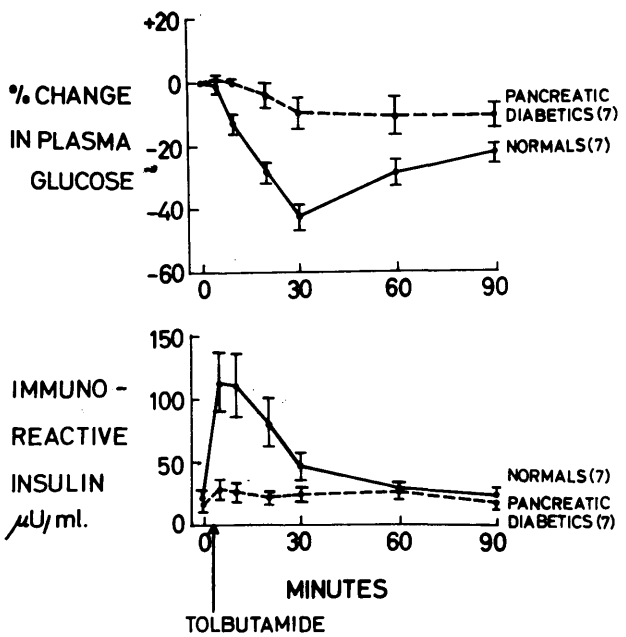

FIG. 1. Effect of intravenous tolbutamide on plasma glucose and serum immunoreactive insulin in normal subjects and pancreatic diabetics (mean ± S.E.M.)

In addition, the mean fasting serum IRI level was not significantly different in the two groups, despite the nearly twofold greater mean fasting plasma glucose level in the pancreatic diabetic patients.

The possibility that factors other than pancreatic disease could have contributed to the poor insulin response after tolbutamide warrants consideration. Five of the patients were taking chlorpropamide prior to testing and a decreased insulin secretory response to glucose after months of therapy has been demonstrated.[9] The changes in insulin levels were generally small; also the drug was discontinued for some days prior to testing in our study to minimize any similar effect. All the pancreatic diabetic patients were lean, and, since obesity leads to hyperinsulinism,[10] it is feasible that leanness per se might be associated with a diminished pancreatic response to insulinogenic stimuli. This point must remain speculative, however, since there is little direct supporting evidence.

Comparison of the insulin responses in pancreatic diabetes with those in "primary" diabetes is of interest. In the light of recent observations,[11-13] a comparable group of middle-aged, nonobese, moderately severe primary diabetics could also be expected to show insulinopenia, although possibly not to the same extent. Indeed the results in our patients approach those reported in juvenile diabetes mellitus after intravenous tolbutamide.[14,15]

Our findings also suggest that the majority of patients with pancreatic diabetes are unlikely to respond well to oral sulfonylurea agents because of their marked insulinopenia. The known unpredictability of the intravenous tolbutamide tolerance test in determining the likely response of patients to oral therapy[16] and the abnormal sensitivity to exogenous insulin that patients with pancreatic diabetes manifest[17] have prompted us, however, to investigate further this problem by means of a controlled trial. Preliminary results unfortunately are not encouraging.

ACKNOWLEDGMENT

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ABSTRACTS

Brown, Charlesta B.; and Civen, Morton (Med. Res. Programs, V.A. Hosp., Long Beach, Calif., and Dept. of Biochem., Univ. of Southern California Sch. of Med., Los Angeles, Calif.): CONTROL OF RAT LIVER AROMATIC AMINO ACID TRANSAMINASES BY GLUCAGON AND INSULIN. Endocrinology *84*:381-85, February 1969.

Glucagon and insulin increase rat liver tyrosine α-ketoglutarate transaminase (TKT) activity, but only the former increases phenylalanine pyruvate transaminase (PPT) activity. Anti-insulin serum (AIS) given in large doses produced an acutely diabetic state with elevation of TKT but depression of PPT values. Exogenous glucagon given to AIS-treated animals raises the levels of both transaminases. The results suggest that glucagon and insulin may have mutually opposing actions in the regulation of these hepatic transaminases. C.R.S.

Brown, J. H.; Riggilo, D. A.; and Dungan, K. W. (Mead Johnson Res. Center, Evansville, Ind.): ORAL EFFECTIVENESS OF BETA ADRENERGIC ANTAGONISTS IN PREVENTING EPINEPHRINE-INDUCED METABOLIC RESPONSES. J. Pharmacol. Exp. Ther. *163*:25-35, September 1968.

The inhibitory effect of various sulfonamidophenethanolamines and other antagonists on catecholamine-induced hyperglycemia and lactic acidosis was examined in conscious dogs and anesthetized rats. Blood glucose response was inhibited by either alpha or beta adrenergic antagonists. Hyperlactic acidemia correlated directly with potency of catecholamines as beta adrenergic stimulators and the response was blocked by specific inhibitors. Phentolamine blocked hyperglycemia due to alpha stimulation but not lactic acidosis due to beta stimulation. Propanolol failed to prevent epinephrine-induced hyperglycemia in dogs but was potent in rats. A.R.C., JR.

Coll-Garcia, E.; and Gill, J. R. (Dept. of Biochem., Univ. of Bristol, Bristol, England): INSULIN RELEASE BY ISOLATED PANCREATIC ISLETS OF THE MOUSE INCUBATED IN VITRO. Diabetologia *5*:61-66, 1969.

Verbatim summary. The release of insulin during incubation of mouse islets of Langerhans, isolated after digestion of the pancreas with collagenase, has been studied, and the influence of various factors on the rate of release investigated. Glucose at 3.0 mg./ml. (high glucose) stimulated insulin release but had no effect at 0.6 mg./ml. (low glucose). Mannoheptulose blocked the stimulation by high glucose, as did adrenaline. The adrenaline effect was abolished by phentolamine, an alpha-adrenergic blocking agent. Glucagon alone, stimulated insulin release, and also with low glucose, but not consistently with high glucose. Adrenaline abolished the stimulation by glucagon. Theophylline stimulated release with low glucose, much less so with high glucose and not at all with glucagon at either glucose concentration. Tolbutamide stimulated release with low glucose, and this effect was not inhibited by adrenaline. The suitability of this preparation for studies of islet cell metabolism and its relationship to secretion of insulin is discussed.

Conn, H. O.; and Elkington, S. G. (Med. Serv., V.A. Hosp., West Haven, Conn., and Dept. of Intern. Med., Yale Univ. Sch. of Med., New Haven, Conn.): LACK OF CORRELATION BETWEEN BLOOD GLUCOSE AND AMMONIA CONCENTRATIONS. Amer. J. Med. Sci. *257*:132-39, February 1969.

The authors studied the effect of orally administered glucose (1.75 gm. per kg.) upon blood ammonia levels and of orally administered ammonium chloride (3 gm.) upon