THE EFFECTS OF EXOGENOUSLY INDUCED HYPERGLUCAGONEMIA IN INSULIN-TREATED DIABETICS

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A recent report that the continuous intravenous infusion of glucagon failed to worsen hyperglycemia in two insulin-treated juvenile diabetics has raised doubts as to the importance of hyperglucagonemia in insulin-treated diabetics. To reexamine this, six juvenile type patients receiving a constant 28 to 50 U/day dose of regular insulin in five doses (before each of four meals and at 1:30 a.m.) were given glucagon subcutaneously for one or two days at 4-hour intervals (four patients) or 2-hour intervals (two patients), raising their mean plasma glucagon levels to an average of 590 ± 15 pg/ml. Mean plasma glucose concentration, measured at 2-hour intervals around the clock, rose from 231 ± 17 mg/dl on the control day to 285 ± 19 pg/ml (p < 0.01) during glucagon administration. Glucose excretion rose significantly above the control value of 42 ± 7 gms per 24 hours to 145 ± 23 gms (p < 0.01) and the excretion of urea nitrogen and ketones also increased significantly during glucagon administration (p < 0.05; p < 0.01, respectively). These data indicate that exogenous hyperglucagonemia can cause metabolic deterioration in insulin-treated diabetics.

INTRODUCTION

Relative hyperglucagonemia is reportedly present in all forms of spontaneous (1, 2, 6, 9) and experimentally induced (7) diabetes and has been implicated in the glucose overproduction that may occur in that disease (11). However, a recent report that infusion of glucagon for 48 hours failed to worsen the hyperglycemia of two insulin-treated juvenile diabetics has cast doubt on glucagon's importance in the presence of insulin (8). This study was designed to reexamine the effects of exogenous glucagon in six insulin-dependent diabetics.

METHODS AND MATERIALS

Six patients with typical juvenile type diabetes mellitus, ranging in age

from 16 to 49 years, were studied in the Clinical Research Unit of Parkland Memorial Hospital. All patients received a constant diet consisting of 40% carbohydrate, 40% fat, and 20% protein with identical meals throughout the study. A constant dose of regular insulin ranging from 28 to 50 U/day was administered in four divided doses 30 minutes prior to meals and, in most patients, a fifth dose was given at 0130 each morning. A placebo injection of normal saline or glucagon (0.2 mg to 0.5 mg) was administered subcutaneously at 4-hour intervals in four patients and at 2-hour intervals in two patients.

Blood was drawn at 2-hour intervals through a 19-gauge butterfly needle in a forearm vein and collected in chilled tubes containing 12 mg EDTA and Trasylol R, centrifuged at 40, and the plasma stored at -20°C until radioimmunoassay for glucagon (3) and, in one patient, for insulin (12). Glucose in plasma and urine was measured with a Beckman glucose analyzer. Measurements of urinary urea nitrogen (4) and β-hydroxybutyrate and acetoacetate excretion (5) were also made.

RESULTS

Effects of subcutaneous administration of glucagon. The mean plasma IRG and glucose concentrations and the 24-hour glucose excretion for all patients before, during, and after glucagon administration are shown in Table 1. The mean plasma glucose concentration rose from 231 ± 17 mg/dl to 285 ± 19 (p <0.01) during glucagon administration. Glucose excretion rose from 42 ± 7 gms per 24 hours to 145 ± 23 gms per 24 hours (p <0.01) during glucagon administration and declined to 56 ± 18 (p <0.01) following its discontinuation. Urinary excretion of urea nitrogen and ketones increased significantly during the period of glucagon administration (p <0.05; Table 2).

The IRG concentration of the group averaged 590 ± 135 pg/ml during the administration of glucagon. Of the 72 glucagon determinations during glucagon administration in the six patients, 50 were less than 1000 pg/ml and 38 were less than 500 pg/ml; the IRG range observed in the portal vein of insulin-deprived