Glucose Management in Patients Undergoing
Operation for Insulinoma Removal

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Medical records of 38 patients undergoing anesthesia and surgery for removal of an insulinoma were reviewed to determine 1) the safety of avoiding intraoperative glucose, 2) the appropriate frequency of plasma glucose analysis, and 3) the accuracy of using rebound hyperglycemia as an indication of tumor removal. Plasma glucose was determined approximately every 15 min during operative and recovery-room periods. The changes in plasma glucose concentrations before tumor removal were compared with those occurring after the resection in each patient by separate linear regressions of glucose concentration *versus* time. The slopes of the preresection regression lines averaged +0.196 (±SD 0.577) mg · dl^{-1} · min^{-1}. The mean of the postresection slopes was +0.624 (±SD 0.339) mg · dl^{-1} · min^{-1}. The mean difference in slope (post- minus pre-) was +0.426 (±SD 0.748) mg · dl^{-1} · min^{-1}, indicating that a significant ($P < 0.02$) increase in post-resection slope had occurred. In no case did a preresection plasma glucose concentration decrease to less than 50 mg · dl^{-1} if the previous value had been 60 mg · dl^{-1} or greater. Nonetheless, there were nine patients whose plasma glucose did decrease to less than 50 mg · dl^{-1} at some time during the operative course. Only 39% of patients showed a rebound of 20 mg · dl^{-1} or more in the first 30 min after resection.

The authors conclude that intermittent sampling is safe as long as plasma glucose is kept above 60 mg · dl^{-1} by infusing glucose. Hyperglycemic rebound is not helpful in determining the adequacy of surgical excision. (Key words: Complications: hypoglycemia. Hormones: insulin. Metabolism: glucose. Surgery: insulinoma.)

GLUCOSE MONITORING AND MANAGEMENT in patients requiring surgery for removal of insulin-secreting pancreatic tumors (insulinomas) is controversial.[1–5] Because dangerous intraoperative hypoglycemia may develop with signs masked by anesthesia, a critical aspect in perioperative management is the monitoring of plasma glucose levels. Another reason to monitor plasma glucose concentrations intraoperatively has evolved since the description in 1951[6] of "hyperglycemic rebound" following complete tumor removal. An increase in plasma glucose values within 30 min after excision has been suggested to be an indicator of total tumor removal.[1,2,7,8]

Various approaches to perioperative glucose management have been described.[1,3,4,7,9,10] The successful use of epidural anesthesia (to detect subjective signs of hypoglycemia in awake patients) with repeated plasma glucose determinations to detect hypoglycemia and hyperglycemic rebound has been reported.[7] Continuous glucose infusions (with intermittent plasma glucose determinations) have been employed to maintain moderate hyperglycemia in an effort to prevent any chance of hypoglycemia intraoperatively.[9] This approach has been criticized because of inability to detect "hyperglycemic rebound" after excision of the tumor.[1] By contrast, others deliberately maintain moderate hypoglycemia intraoperatively using non-glucose-containing iv solutions and intermittent glucose determinations.[1–3] This technique is favored by those who consider it important to detect "hyperglycemic rebound" after tumor excision. Concerns with this technique are 1) the possibility of developing dangerous hypoglycemia between measurements, and 2) a recent report of falsely negative responses when using hyperglycemic rebound as an indicator of tumor removal.[3] A recent development in the management of patients with insulinomas has been the artificial pancreas (Biostater®).[10–12] This device continuously monitors plasma glucose concentrations and can administer either glucose or insulin to maintain plasma glucose in a predetermined range. The machine has the disadvantages of being complex, expensive, large, and requiring an experienced operator in its use.[11]

This report reviews our experience with use of non-glucose-containing iv solutions and intermittent glucose determinations in the perioperative period in 38 patients who underwent operation for removal of insulinomas. The objectives of this report are to determine 1) whether intermittent glucose determinations are sufficient to prevent severe hypoglycemia during insulinoma resection; 2) the degree and predictability of hypoglycemia occurring during rigid adherence to use of non-glucose-containing iv solutions; and 3) if hyperglycemic rebound occurs consistently enough to be useful in determining the success of resection, and, therefore, to justify the maintenance of deliberate hypoglycemia intraoperatively.

Materials and Methods

Forty-four patients underwent surgical excision of insulinoma(s) between 1977 and 1981 at the Mayo Clinic. Six of these patients were not included in this
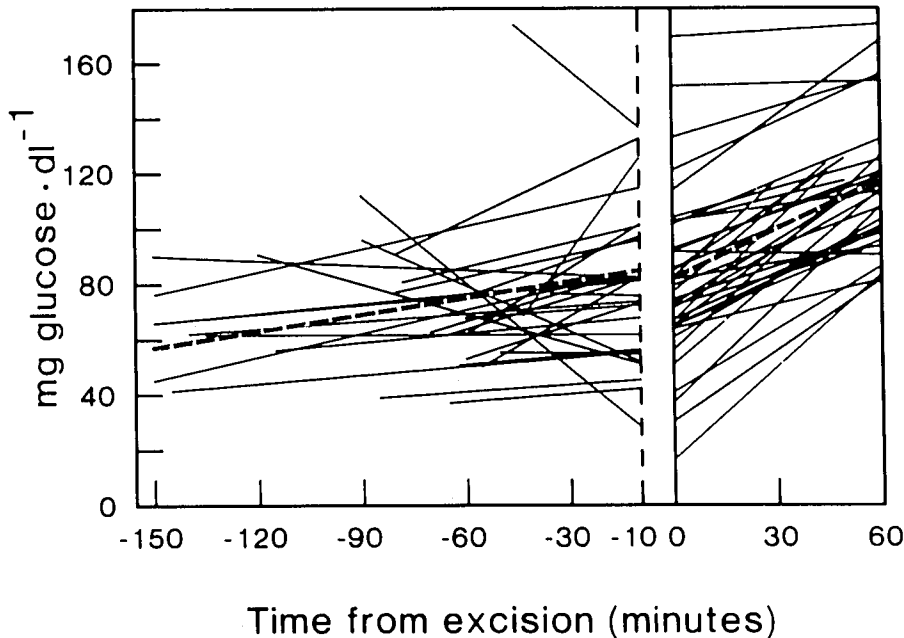
FIG. 1. The calculated preresection and postresection regression lines for each patient are shown. The mean preresection and post-resection lines are indicated by the heavy lines.

report for the following reasons. In three cases, the complete records of intraoperative and postoperative glucose determinations could not be located. Two patients were excluded because hypoglycemia had developed early in their operative course and they received intravenous glucose infusions. The data from these two patients could not be used in the analysis. In one case the anesthesiologist and surgeon elected not to use the moderate hypoglycemic approach, and glucose was infused throughout anesthesia and surgery.

All patients were given nothing by mouth after a light snack 8 h before surgery. Dextrose infusions were discontinued 2 h before induction of anesthesia in those patients receiving them. Diazoxide, if taken previously was discontinued 2 or 3 days before operation, because this agent will increase plasma glucose determinations. Plasma glucose was measured prior to induction of anesthesia and thereafter approximately every 15 min during the perioperative period. The sampling interval had a range of 5–40 min at the attending anesthesiologist's discretion. Samples were measured immediately with a Beckman glucose analyzer by a technician who was present in the surgical suite.[13] After a thiopental induction, all patients were anesthetized with nitrous oxide and enflurane. The time of tumor excision, if there was a single adenoma, or the time of removal of the pancreas, if a partial pancreatectomy was performed, was designated as time zero for purposes of computing individual linear regression lines. Negative numbers designate the times of blood sampling prior to the surgical excision, whereas sampling times follow-

ing tumor removal or partial pancreatectomy were designated with positive numbers. Preresection and postresection measurements in each patient were evaluated by constructing linear regression lines for plasma glucose concentrations *versus* time. There were sufficient data to determine a preresection regression line in each of 37 patients and a post-resection regression line in 37 patients. It was possible to calculate both in 36 patients. Because the linear correlation coefficient (r) is slope dependent, and therefore not useful when slopes are near zero, $Sy \cdot x$ (defined as the standard deviation of the points about the regression line and measured in mg glucose $\cdot$ dl^{-1}) was used to depict goodness of fit.[14] The mean of the slopes of the 37 preresection regression lines and the mean of the 37 postresection regression lines were tested against zero slope using a single sample, two-tailed t test. The postresection and preresection regression lines were compared by summarizing the individual differences in slope (post- minus pre-) using a period two-tailed t test. $P < 0.05$ was considered significant.

Results

The mean of the slopes of the 37 individual patient preresection regression lines was $+0.196$ ($\pm$SD 0.577) mg $\cdot$ dl^{-1} $\cdot$ min^{-1} (fig. 1). This was significantly greater than zero ($P < 0.05$), indicating a slight but definite increase in plasma glucose before a tumor excision, despite no iv glucose. The median $Sy \cdot x$ of the preresection regression lines was 7.11 mg $\cdot$ dl^{-1}. This shows that

the fit of calculated regression lines was good. Nonetheless, there were 10 patients (27%) in whom preresection regression lines had negative slopes, indicating a decrease in plasma glucose prior to tumor excision.

The mean of the slopes of the 37 postresection regression lines was $+0.624$ ($\pm$SD 0.339) mg·dl^{-1}·min^{-1} (fig. 1). This was significantly greater than zero ($P = 0.0001$). The median Sy·x of the postresection regression line was 6.86 mg·dl^{-1}. There was only one patient whose postresection regression line had a negative slope (-0.02 mg·dl^{-1}·min^{-1}), indicating a decline in plasma glucose after tumor removal. Despite this, the resection subsequently was proved to have been curative. The only patient in this series not cured surgically showed a typical hyperglycemic response in the postresection period (slope $+ 0.813$ mg·dl^{-1}·min^{-1}; fig. 2).

The difference in the slopes of postresection and preresection regression lines (post- minus pre-) were calculated for each of 36 patients. The mean difference in slope was $+0.426$ ($\pm$SD 0.748) mg·dl^{-1}·min^{-1}. The group average post-slope was significantly greater ($P < 0.002$) than that for the pre-slope. In 30 patients, the change in slope was positive indicating the expected finding, namely that plasma glucose increased at a faster rate following tumor resection (fig. 3). In six patients, despite subsequent evidence that no residual tumor was present, the change in slope was negative nonetheless. In these six patients, the rate of plasma glucose increase was greater before resection than afterward.

There were 526 plasma glucose measurements, 253 preresection and 273 postresection. Only four preresection glucose values showed a decrease of more than 20 mg·dl^{-1} from the immediately preceding measurement (table 1). In a total of 38 patients in whom glucose administration was avoided, there were nine who had a plasma glucose of 50 mg·dl^{-1} or less at some time during the perioperative course. There were only two instances wherein plasma glucose decreased to less than 50 mg·dl^{-1} if the preceding value was 55 mg·dl^{-1} or higher (57 mg·dl^{-1} to 44 mg·dl^{-1}: 55 mg·dl^{-1} to 48 mg·dl^{-1}). There were no instances of plasma glucose concentrations less than 50 mg·dl^{-1} if the immediately preceding value was 60 mg·dl^{-1} or higher. Only 15 of the 38 patients showed an increase in plasma glucose of 20 mg·dl^{-1} or greater when the sample taken closest to tumor resection was compared with that taken closest to 30 min after resection.

Discussion

There are contrasting approaches to the perioperative management of glucose in patients undergoing resection of insulinoma.[1,3–5,10] Roizen suggested that in-
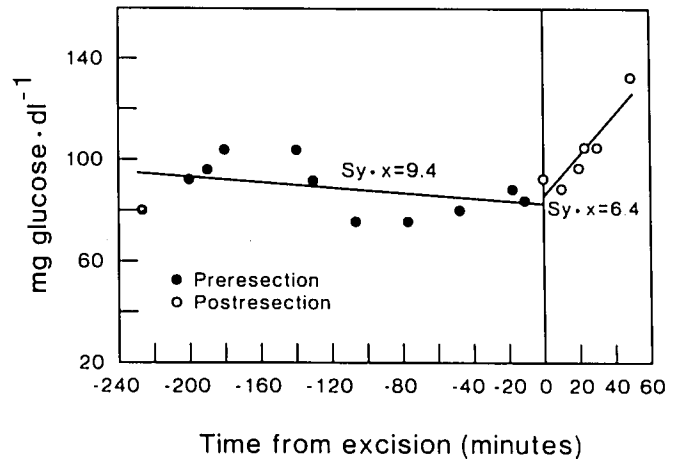

FIG. 2. The data points and regression lines are shown for the only patient not surgically cured. The difference in slope (post- minus pre-) was 0.87 mg·dl^{-1}·min^{-1}.

sulinoma surgery by performed only in institutions that have an artificial pancreas (Biostater®) available for on-line glucose analysis and glucose and/or insulin infusions as needed.[4] Pender and Basso contended that glucose administration is not mandatory but that plasma glucose levels should be monitored at "frequent intervals" during the operation.[5] Suffecool suggested that patients not be given glucose intraoperatively unless the plasma glucose is less than 50 mg·dl^{-1} and that the intermittent measurement of glucose (every 15 min) is satisfactory.[1] He also suggested that a prompt rise (30 min) in plasma glucose following excision of the tumor may be taken as presumptive evidence of adequate resection. By contrast, Tutt et al.[3] showed that one-fourth
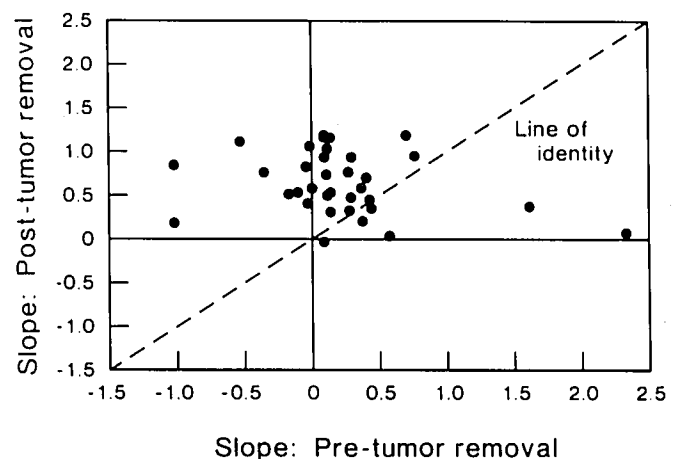

FIG. 3. The preresection and postresection slopes are plotted for the 36 patients in whom both could be calculated. The six points to the right of the line of identity show a negative (post- minus pre-) difference in slope.

TABLE 1. Preresection Measurements That Showed a Decrease of More than 20 mg·dl⁻¹ from the Preceding Value

174 mg·dl⁻¹ to 143 mg·dl⁻¹
118 mg·dl⁻¹ to 90 mg·dl⁻¹
85 mg·dl⁻¹ to 57 mg·dl⁻¹
82 mg·dl⁻¹ to 59 mg·dl⁻¹

of their patients failed to exhibit a hyperglycemic rebound until 90 min or more after tumor excision, implying that hyperglycemic rebound may not be of value in the operating room.

Enflurane and halothane may cause hyperglycemia by inhibiting pancreatic insulin release.[15,16] Gingerich et al.[15] reported that halothane in a concentration of 0.33 mM (1.5 MAC) decreased glucose-stimulated insulin release in rat pancreatic islets by 33%. Ewart et al.[16] demonstrated that enflurane, again in rat pancreatic islets, produced a dose-related decrease in glucose-stimulated insulin release. In fact, at 1.18 MAC enflurane (0.47 mM) there was a 50% decrease in insulin release. The effects of these anesthetics on active insulin-producing tumors are not known. The studies above suggest that enflurane may be the anesthetic of choice in patients who have insulin-producing tumors, because the inhibition of insulin release was greater with enflurane than with halothane. All patients in the current series were anesthetized with enflurane. It is possible that our patients had resultant higher plasma glucose concentrations with enflurane anesthesia than they might have had with halothane anesthesia.

There are three controversial questions regarding glucose management in the patient with insulinoma. First, is intermittent sampling of plasma glucose adequate to protect patients from hypoglycemia? Second, does maintenance of moderate hypoglycemia by deliberately withholding intravenous glucose expose patients to dangerous hypoglycemia? Third, is hyperglycemic rebound consistently present, and if so, may it be taken as evidence of adequate surgical resection?

In the 253 preresection plasma glucose measurements, there were only four instances in which there was a decrease of more than 20 mg·dl⁻¹ from one measurement to the next, the next taken approximately 15 min later. None decreased to less than 50 mg·dl⁻¹. There were two instances of plasma glucose concentrations less than 50 mg·dl⁻¹ if the preceding value had been greater than 55 mg·dl⁻¹. There were no cases wherein plasma glucose decreased to less than 50 mg·dl⁻¹ if the preceding plasma glucose was 60 mg·dl⁻¹ or greater. This suggests that intermittent sampling of plasma glucose is satisfactory as long as the patient's plasma glucose is kept at 60 mg·dl⁻¹ or higher. There were nine patients whose plasma glucose was less than

50 mg·dl⁻¹ during the preresection period. A diagnosis of hypoglycemia usually is justified if plasma glucose falls below 50 mg·dl⁻¹.[17] Rigidly adhering to the "moderate" hypoglycemic technique by not administering intravenous glucose may expose some patients to dangerous hypoglycemia during operation.

In the 37 patients in whom postresection data could be evaluated, there was a mean increase of 0.62 mg glucose·dl⁻¹·min⁻¹ after tumor resection. However, the large standard deviation (0.339 mg·dl⁻¹·min⁻¹) indicates that any hyperglycemic response after resection is variable and may not present for some time, in agreement with Tutt et al.[3] Additionally, we did have one patient who showed a hyperglycemic response immediately after resection, who nonetheless had a functioning tumor eventually proven to remain. Only 15 of 38 patients (39%) in our series showed an increase in plasma glucose of 20 mg·dl⁻¹ or greater when the time closest to tumor resection was compared with the time closest to 30 min after resection. This indicates that hyperglycemic rebound probably is not of clinical value.

In conclusion, it appears that 1) intermittent sampling of plasma glucose is adequate to protect patients from dangerous hypoglycemia as long as plasma glucose is kept above 60 mg·dl⁻¹; 2) maintenance of moderate hypoglycemia by withholding intravenous glucose during operation may expose patients to dangerous hypoglycemia; and 3) although there may be eventual hyperglycemic rebound, it is of no predictive value for individual patients in the operating room, and false-positive results may even occur.

Why not abandon the moderate hypoglycemic approach, start an intravenous glucose infusion, and maintain plasma glucose in a range of 100–150 mg·dl⁻¹? The moderate hypoglycemia approach has been preferred by some surgeons and anesthesiologists in an attempt to use a postresection increase in plasma glucose concentration as an indication of successful tumor removal. We recommend that iv glucose *not* be withheld from patients undergoing operations for removal of insulinoma(s). Withholding glucose may result in potentially dangerous hypoglycemia. Hyperglycemic rebound is not helpful because false-negative responses are common and false-positive responses may occur. We also recommend that plasma glucose be monitored every 15 min and the glucose infusion adjusted to maintain plasma glucose levels above 60mg·dl⁻¹.

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