Gluco-regulatory Response to Intravenous Glucose Infusion in Children Undergoing Surgery

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Surgery is usually combined with intravenous glucose infusion to meet short-term energy requirements. Previous data on the metabolic response to parenteral glucose administration are controversial. In normal adults, intravenous infusion of glucose at a rate of 3.5 $mg \cdot kg^{-1} \cdot min^{-1}$ has been shown to produce a progressive increase in plasma glucose concentration up to 60 min, which remains stable thereafter for the subsequent 60 min.[1] At the same time, the plasma insulin level increased by 200% and the plasma glucagon concentration fell by 25%. In adult patients, the continuous infusion of glucose at a rate of 1.5 $mg \cdot kg^{-1} \cdot min^{-1}$ during surgery has been reported to be associated with a 100–200% increase in blood glucose concentration at 5 h,[2] insulin secretion being simultaneously suppressed. Subsequently, a marked elevation in the plasma insulin level in combination with a reduction of the high blood glucose concentration was found. Increased plasma glucagon levels have been observed during surgery in adult patients.[3] There is also evidence that erythrocyte insulin binding is inhibited postoperatively in adult subjects who received a glucose infusion during surgery, suggesting a perioperative development of insulin resistance at the receptor level.[4] Limited data on the metabolic response to parental glucose loading in conjunction with surgery in children are available. We undertook the present study to evaluate the effect of surgical stress on the gluco-regulatory response to intravenous glucose infusion and on the insulin sensitivity at the receptor level in children.

PATIENTS AND METHODS

Twenty children (seven boys) with a mean age of 5.0 (3.6; SD) yr (range 1.1–14.2 yr) were studied. All were of normal weight (relative weight 83–116% of the expected weight for height) and in good health, apart from the indication for surgery. To standardize the surgical trauma the children all underwent a ureteroplastic procedure of the same magnitude performed by the same surgeon. The children fasted for 6 h before induction of anesthesia. After premedication with rectal diazepam (0.5 mg/kg)[5] and atropine (0.03 mg/kg),[6] anesthesia was induced with thiopental (5 mg/kg iv) and maintained with 70% nitrous oxide in oxygen, fentanyl (2 µg/kg iv), and alcuronium (0.25 mg/kg iv). The average length of surgery was 120 (38; SD) min. Buprenorphine (5 µg/kg) was given intramuscularly at six hourly intervals, as required for postoperative analgesia. The mean dose given during the day of operation was 9.4 (4.5; SD) $µg \cdot kg^{-1}$ (range 4.6–17.3 $µg \cdot kg^{-1}$). The patients received Ringer's solution (28 mmol acetate $\cdot l^{-1}$) and 5% dextrose (Ringer-steril c.glucos 5%®, Medipolar, Oulu, Finland) 8 ml $\cdot kg^{-1} \cdot h^{-1}$ (6.6 mg glucose $kg^{-1} \cdot min^{-1}$) during anesthesia and 0.3% saline solution and 5% dextrose (Natrosteril III 0.3% c.glucos 5%®, Medipolar, Oulu, Finland) 4 ml $\cdot kg^{-1} \cdot h^{-1}$ (3.3 mg glucose $kg^{-1} \cdot min^{-1}$) thereafter until the following morning. Blood transfusions were not given to any patient.

Blood samples for laboratory measurements were drawn preoperatively and 2 and 4 h after the commencement of anesthesia and on the first postoperative morning. Hemoglobin, hematocrit, serum osmolality, and serum sodium and potassium concentrations were determined using routine laboratory techniques. Plasma acetoacetate and betahydroxybutyrate concentrations were analyzed using the kinetic enzymatic method of Hansen and Freier, with some modifications.[7] Blood glucose concentration was measured using a hexokinase method (Glucoqvant®, Boehringer Mannheim, Mannheim, FRG).

Blood samples (10 ml) for radioimmunological determinations were collected into cooled heparinized tubes containing 2,500 units of aprotinin (Apronin®, Medica, Helsinki, Finland). Plasma was frozen for subsequent analysis of immunoreactive insulin (IRI), C-peptide, and

TABLE 1. Laboratory Data, Mean (SD), in 20 Children Preoperatively, 4 h after the Initiation of Anesthesia,
and on the First Postoperative Morning

	Preop.	4 h	1 Postop. Morning
B-Hemoglobin, g/100 ml	12.4 (1.2)	11.7 (1.3)*¶	11.0 (1.3)†¶ and ‡§
B-Hematocrit, packed cell vol	0.36 (0.03)	0.34 (0.03)*¶	0.32 (0.03)†¶ and ‡¶
S-Sodium, mmol/l	142 (2.5)	142 (1.3)	139 (2.8)†¶ and ‡¶
S-Potassium, mmol/l	4.0 (0.4)	3.7 (0.3)	4.0 (0.2)‡¶
S-Osmolality, mosm/kg	289 (6.2)	293 (8.8)*§	285 (10)‡§
P-Acetoacetate, mmol/l	0.22 (0.15)	0.30 (0.29)	0.37 (0.26)†§
P-Beta-hydroxybutyrate, mmol/l	0.52 (0.44)	0.54 (0.74)	0.57 (0.55)

B = blood; S = serum; P = plasma
Comparison between the samples: *preop. vs. 4 h; †preop. vs. 1

postop. morning; ‡4 h vs. 1 postop. morning.
Level of significance: §$P < 0.05$; ¶$P < 0.01$.

glucagon. Plasma IRI concentrations were measured using antiserum M 8309 (Novo Research Institute, Bagsvaerd, Denmark), with a minor modification of the charcoal separation method described by Herbert et al.[8] The sensitivity of the assay was 1 mU/l and the coefficient of interassay variation 8.4% over a concentration range from 5–50 mU/l. Plasma C-peptide concentrations were determined according to Heding,[9] using antiserum M 1230 (Novo Research Institute). The sensitivity of the assay was 0.02 nmol/l and the interassay coefficient of variation 10% at concentrations ranging from 0.10–1.00 nmol/l. The concentrations of pancreatic glucagon were analyzed according to Heding's method,[10] using the C-terminal specific antiserum K 5563 (Novo Research Institute). The sensitivity was 10 ng/l and the interassay variation 16% over a concentration range from 20–150 ng/l. The concentrations of glucagon-like immunoreactivity (GLI = pancreatic glucagon + enteroglucagon) were measured using the N-terminal specific antiserum K 4023 (Novo Research Institute).[10] The sensitivity was 15 ng/l and the interassay coefficient of variation 12% at concentrations ranging from 50–300 ng/l. The concentrations of enteroglucagon were obtained by subtracting the concentrations of pancreatic glucagon from the concentrations of GLI.

For determination of ^{125}I-insulin binding to erythrocytes, the method of Gambhir et al.[11] was used, with some modifications.[12] Specific insulin binding was defined as total minus nonspecific binding, the latter determined by obtaining the values in the presence of 10^5 ng/ml unlabeled insulin. The amount of insulin specifically bound was corrected to a final erythrocyte concentration of 3.52×10^9 cell/ml. The non-specific binding was about 10–17% of the total binding (1.1–1.9% of the total radioactivity). Binding data were analyzed using the Scatchard plot, and the average affinity profile was determined using the method of De-Meyts and Roth,[13] in which the highest insulin concentration used for calculation was 100 ng/ml. The insulin binding to erythrocytes was studied in only 13 children

(mean age 5.7, 4.0; SD years) since, in seven children, the available sample volume in one of the two samples was found to be insufficient for binding determinations.

Urine was collected for 24 h postoperatively, and analyzed for glucose using the hexokinase method (Boehringer Mannheim) and for acetoacetate and acetone using Ketostix (Ames Company, Elkhart, Indiana).

Statistics. The data was statistically evaluated using the one-way analysis of variance for repeated measures or the two-way analysis of variance for repeated measures on one factor or the Student's paired t test. The Bonferroni correction of the unpaired t test was used for subsequent comparisons between two groups and the Bonferroni correction of the paired t test for comparison between the samples, as necessary. The criterion for the rejection of the null hypothesis was a two-tailed P value of less than 0.05.

RESULTS

Blood hemoglobin, hematocrit ($P < 0.01$), and serum sodium ($P < 0.01$) decreased, and serum osmolality and plasma acetoacetate ($P < 0.05$) increased, after surgery (table 1). There were no significant changes from the preoperative level in the mean values of serum potassium, and plasma beta-hydroxybutyrate concentration during the postoperative follow-up. Blood glucose ($P < 0.01$), plasma IRI ($P < 0.05$), and C-peptide ($P < 0.05$) concentrations all increased 2–4 hours after the commencement of anesthesia (table 2). On the first postoperative morning, the values were decreased from the peak level, but the blood glucose ($P < 0.01$) and C-peptide ($P < 0.05$) concentrations were still higher than those observed preoperatively. The molar ratio of C-peptide to IRI remained unchanged. The only alteration in the pancreatic glucagon levels was a decline 2 h after the initiation of anesthesia. Plasma enteroglucagon concentration did not change from the preoperative level during the day of operation, but it was significantly ($P < 0.01$) lower on the next morning than preoperative value.

TABLE 2. Blood Glucose, Plasma IRI, and C-peptide Concentrations, Molar Ratio of C-peptide to IRI and Plasma Pancreatic Glucagon, and Enteroglucagon Levels, mean (SD), Preoperatively, 2 and 4 h after the Initiation of Anesthesia, and on the First Postoperative Morning in 20 Children

	Preop.	2 h*	4 h	1 Postop. Morning
Blood glucose, mmol/l	4.19 (0.49)	7.33 (1.50)† ††	7.63 (1.75)‡ ††	5.14 (1.02)§ †† and ¶ ††
IRI, mU/l	9.1 (6.9)	22.1 (18.1)† **	21.7 (22.5)‡ **	16.3 (13.1)
C-peptide, nmol/l	0.20 (0.20)	0.54 (0.44)	0.44 (0.52)‡ **	0.33 (0.28)§ **
C-peptide/IRI, molar ratio	3.49 (1.28)	3.27 (1.71)	3.19 (1.57)	3.44 (1.71)
Pancreatic glucagon, ng/l	73.8 (27.6)	46.7 (12.7)† ††	76.5 (41.2)	64.0 (28.3)
Enteroglucagon, ng/l	123.8 (47.8)	83.3 (62.0)	118.0 (63.5)	85.5 (38.2)§ †† and ¶ **

* Statistical analysis has been carried out separately for a group of nine patients.

Comparison between the samples: †preop. vs. 2 h; ‡preop. vs. 4 h;

§preop. vs. 1 postop. morning; ¶4 h vs. 1 postop. morning.

Level of significance: **P < 0.05; ††P < 0.01.

The insulin binding to erythrocytes, the number of insulin receptors, and average affinity constants were not significantly different after surgery than those seen preoperatively (fig. 1; table 3). Glucose was found in the 24-h urine samples (maximum 7.5 mmol) in six children. No differences in mean age or in pre- and postoperative blood glucose, plasma acetoacetate, beta-hydroxybutyrate, IRI, C-peptide, pancreatic glucagon, and enteroglucagon concentrations, or in the molar ratio of C-peptide to IRI, were found between the subjects with and without glucosuria.

A positive Ketostix reaction in postoperative urine samples were observed in eight children. There was no significant difference in age between those with ketonuria (4.4 ± 4.3 yr) and those without ketonuria (5.3 ± 2.5 yr). Plasma acetoacetate and beta-hydroxybutyrate levels were higher (P < 0.01) both pre- and postoperatively in children with ketonuria than in those without ketonuria (table 4). No significant increase from the preoperative level was found postoperatively in either determination.

Blood glucose and plasma IRI, C-peptide, pancreatic glucagon, and enteroglucagon concentrations were not significantly different pre- and postoperatively when comparing children with and without ketonuria. The molar ratio of C-peptide to IRI was significantly (P < 0.01) higher (4.26 ± 1.63 vs. 2.31 ± 1.07) in children with ketonuria than in those without ketonuria 4 h postoperatively. Erythrocyte insulin binding data, both pre- and postoperatively, were similar in children with and without glucosuria, and in those with and without ketonuria.

DISCUSSION

The present observations suggest that urological surgery during thiopental-nitrous oxide-fentanyl anesthesia does not hinder the pancreatic insulin and glucagon response to intravenous glucose loading in children. This implies that parenteral glucose administration is safe in young individuals during surgery, since physiological changes in the release of pancreatic hormones aim at maintaining normoglycemia. Surgery in combination with perioperative glucose infusion does not seem to alter the metabolic clearance of insulin. The absence of a decrease in insulin removal may protect the patients from hyperinsulinemia in the peripheral circulation and concomitant hypoglycemia. Peripheral insu-
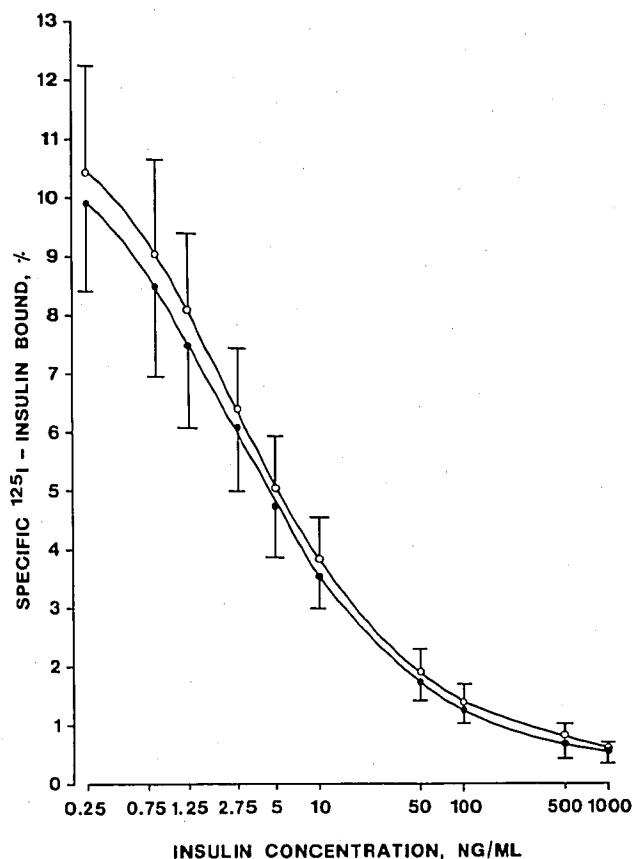

FIG. 1. Pre- (●) and postoperative (O) ^{125}I-insulin binding to erythrocytes in 13 children.

TABLE 3. Mean (SD) Number of Insulin Receptors and Average Affinity Constants Preoperatively and on the First Postoperative Morning in 13 Children

	Preop.	1 Postop. Morning
Number of binding sites/cell	67.7 (12.6)	72.7 (14.7)
K_e (empty site affinity) $\times 10^8$ M^{-1}	2.99 (0.61)	3.03 (0.59)
K_f (full site affinity) $\times 10^8$ M^{-1}	0.74 (0.15)	0.79 (0.17)

lin resistance developing in the perioperative period could result in hyperglycemia. The unchanged insulin binding in combination with similar pre- and postoperative receptor concentrations and affinity constants observed in this study may prevent the possible manifestation of perioperative hyperglycemia in pediatric patients.

Surgical stress itself has been shown to increase the blood glucose level in adult patients without a concomitant rise in the plasma insulin concentration.[14,15] In children not receiving a glucose infusion, a wide scatter in blood glucose values has been found during the perioperative period.[16,17] Postoperative changes in blood glucose, plasma IRI, and glucagon concentrations in our children paralleled those seen in adult volunteers to whom a continuous glucose infusion was administered without surgery.[1,18] Accordingly, a rise in the blood glucose level was associated with an immediate increase in the plasma IRI concentration. Our observations are in contrast to those of Äärimaa et al.,[2] who reported a suppression in insulin secretion 4–5 h after the initiation of surgery in adults who were given a constant glucose infusion. These authors suggested that this sup-

TABLE 4. Plasma Acetoacetate and Beta-hydroxybutyrate Levels, Mean (SD), Preoperatively, 4 h after the Initiation of Anesthesia and on the First Postoperative Morning in Children With and Without Postoperative Ketonuria

	With Ketonuria (n = 8)	Without Ketonuria (n = 10)*
P-Acetoacetate, mmol/l		
Preop.	0.34 (0.15)	0.15 (0.11)†
4 h	0.51 (0.37)	0.16 (0.08)†
1 Postop. morning	0.60 (0.20)	0.19 (0.13)‡
P-Beta-hydroxybutyrate, mmol/l		
Preop.	0.93 (0.39)	0.24 (0.16)‡
4 h	1.07 (0.93)	0.17 (0.19)†
1 Postop. morning	1.02 (0.49)	0.22 (0.36)†

* Data for two children incomplete and omitted.
Comparison between the groups: †p < 0.01; ‡p < 0.001.

pression may be due to the action of epinephrine, which competes with glucose for the glucose receptors[19] leading to insensitivity of the pancreas to glucose. Walsh et al.[20] have shown, however, that a glucose load of 5 $mg \cdot kg^{-1} \cdot min^{-1}$ can significantly increase the plasma insulin concentration in adults during surgery, as compared to the preoperative level. Thus, the finding indicates that the inhibition of insulin secretion can be overcome by a sufficiently high blood glucose concentration. A possible explanation for the discrepancy between our results and those of Äärimaa et al.[2] may be that the glucose load per kg body weight was considerably higher in our children than in their adult patients.

A rise in blood glucose concentration during the perioperative period may also be due to corticosteroids which participate in the regulation of glucose metabolism inhibiting glucose uptake in peripheral tissue.[21] Thus, hypercortisolemia induced by operative stress may be one reason for the hyperglycemia seen during and after surgery.

The modifying effect of anesthetic agents and anesthesia methods on blood glucose regulation during surgery is difficult to estimate because of the powerful influence of surgical stress on glucose metabolism. In adults given a glucose infusion, the blood glucose level increased during thiopental-nitrous oxide-relaxant anesthesia, but the plasma insulin level remained unchanged.[18] In unanesthetized control patients, the plasma insulin level increased significantly, however. This suggests that these anesthetic agents prevented the normal rise in plasma insulin level found after glucose loading. Although many anesthetic agents themselves have no influence on blood glucose and plasma insulin levels,[22-25] their effects on the gluco-regulatory response to a glucose load are unknown. However, anesthetic agents do not ordinarily modify the gluco-regulatory response caused by surgical trauma.[2,22-25]

No alterations occurred in the molar ratio of C-peptide to IRI postoperatively. The molar ratio is determined by the balance between the elimination rates of C-peptide and insulin from the circulation. C-peptide is predominantly metabolized and, to a degree, excreted by the kidneys, whereas the liver is the primary organ of insulin degradation.[26] During the first pass, 50–60% of the portal insulin is extracted by the liver. Accordingly, the molar ratio of C-peptide to IRI reflects the hepatic degradation of insulin, the ratio decreasing concurrently with hepatic extraction.[27] Oral glucose ingestion has been reported to result in a diminished molar ratio, while intravenous glucose administration decreases the molar ratio only initially, and to a lesser extent than oral intake.[28] Our observations suggest that surgery combined with intravenous glucose infusion has no effect on

the metabolic clearance of insulin, including hepatic extraction.

The lowest postoperative blood glucose value in the present study was 3.7 mmol/l, in spite of the continuous glucose infusion (3.3 mg·kg^{-1}·min^{-1}), and the highest was 10.6 mmol/l. The two children (3.5 and 4.5 yr of age) with the lowest postoperative blood glucose levels also had low (3.6 mmol/l and 3.3 mmol/l) preoperative blood glucose values. Low pre- and postoperative blood glucose concentrations have been found in marasmic children,[17] but all the children in the present study were of normal weight. Our results indicate that there is a great individual variation in postoperative blood glucose levels after the same magnitude of surgical trauma in children given the same amount of glucose per kg body weight as a continuous infusion.

Various glucagon responses to surgical trauma have been reported in adult patients not given glucose parenterally.[3,15,29] present results suggest that either glucagon does not function as a stress hormone in children, or that the glucagon response to surgery is inhibited by the glucose load,[15] or by premedication and anesthesia, as reported by Miyata et al.[29] The decrease in the circulating enteroglucagon levels seen on the first postoperative morning is probably due to the interruption of the enteral feeding for at least 30 h.

Eight children in our series showed a positive urinary Ketostix reaction after surgery. These children had higher plasma acetoacetate and beta-hydroxybutyrate levels both pre- and postoperatively than the children without ketonuria. A higher molar ratio of C-peptide to IRI was also found postoperatively in ketonuric children, indicating an augmented hepatic extraction of insulin. The reasons for ketonuria in these children are unclear. Children who developed postoperative ketonuria may have depleted glycogen stores preoperatively and, therefore, relied on lipid metabolism for energy.[30] The occurrence of postoperative ketonuria, however, did not correlate with the blood glucose levels in our patients. The glucosuria observed in some children seems to reflect a low renal threshold for glucose rather than hyperglycemia, as there was no difference in the blood glucose concentrations between the subjects with and without glucosuria.

The present study showed no significant changes from the preoperative level in the insulin binding to erythrocytes, in the number of insulin receptors, and in the average affinity constants after surgery in children. Kaukinen et al.[4] reported that the number of receptors, as well as the receptor affinity for insulin at physiological concentrations, decreased after surgery in adult patients receiving a glucose load. They concluded that the alterations in the receptor characteristics indicate the development of insulin resistance at the receptor level due to the down-regulation phenomenon. The down-regulation hypothesis does not, however, explain the discrepancy between our observations and those of Kaukinen et al. The amount of glucose given postoperatively per kg body weight in an hour was similar in both studies. In addition, average affinity constants and receptor concentrations in the human erythrocyte model have been shown to be of similar magnitude in children over 1 yr of age and in adults.[12] The discrepancy may be due to the various timings of sample collection and/or differences in the degree of surgical stress reaction. On the other hand, no correlation has been found previously between the erythrocyte insulin binding characteristics, blood glucose concentrations, and plasma levels of IRI.[12] Glucose loading has even been reported to increase the affinity of the erythrocyte insulin receptors in normal subjects.[31] In summary, the present study does not provide any evidence of postoperative insulin resistance at the receptor level in children.

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Comparison of Ketanserin and Sodium Nitroprusside in Patients with Severe ARDS

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Pulmonary artery hypertension (PAH) due to an increased pulmonary vascular resistance is a common event in adult respiratory distress syndrome (ARDS).[1]

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PAH increases right ventricular afterload, and may lead to right ventricular dysfunction.[2] Moreover, PAH enhances the accumulation of extravascular lung water[3] by increasing the net microvascular filtration pressure.[4] Because of these potentially deleterious effects, therapy with vasodilators, especially with sodium nitroprusside (SNP), has been attempted both in animal models[5] and in patients with ARDS.[6,7] The clinical use of vasodilators has been limited, however, because pulmonary vasodilation usually impairs gas exchange.

Serotonin, which is released by activated platelets, is a putative mediator of PAH associated with ARDS,[8] because pulmonary platelet entrapment can occur in acute respiratory failure.[9] Ketanserin, a specific receptor antagonist of serotonin,[10] is able to moderately decrease pulmonary artery pressure (PAP) when infused in patients with ARDS.[11,12] Surprisingly, the hemodynamic changes occurred without the expected detrimental effects on gas exchange. To further explain the hemodynamic and gas exchange alterations induced by ketanserin, we used pulmonary artery catheterization and the multiple inert gas elimination technique to define gas