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Baseline insulin/glucose ratio as a marker for the clinical course of hyperglycemic critically ill children treated with insulin

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ABSTRACT

Objective: The objective of this study was to investigate the relations of baseline insulin/glucose ratio to the clinical course of critically ill children. Such information will provide insight into the pathophysiologic mechanisms leading to hyperglycemia and will optimize preventive and therapeutic measures for hyperglycemia in critically ill children.
Methods: Sixty-four consecutively admitted critically ill children with hyperglycemia, defined as a blood glucose level higher than 8 mmol/L (>145 mg/dL) and treated with insulin according to a glucose-control protocol, were included. Demographic data and clinical and laboratory parameters were collected. Insulin sensitivity was investigated by calculating the ratio of insulin to the blood glucose level just before the start of insulin administration. Results are expressed as median (range).
Results: Sixty-four children (24 girls) 7.0 y of age (0.3–16.9 y) with various diagnoses were included. A hyperinsulinemic response, indicated by an increased insulin/glucose ratio (>18 pmol/mmol), was seen in 55% of children. The durations of insulin therapy, mechanical ventilation, and pediatric intensive care unit length of stay in children with a hyperinsulinemic response were longer than in children with a hypoinsulinemic response.
Conclusion: Hyper- and hypoinsulinemic responses play a role in the occurrence of hyperglycemia in critically ill children. Each is associated with a particular clinical course after the initiation of insulin therapy. It would be worthwhile to further investigate if the insulinemic response to hyperglycemia, determined by the insulin/glucose ratio in combination with the type of organ dysfunction, could be used in clinical practice to determine the need for insulin therapy.

Introduction

Critical illness is associated with many endocrine, metabolic, and immunologic changes [1]. One of these is hyperglycemia, which is caused by a complex interaction of endogenous and exogenous factors. Hepatic insulin resistance, the resulting excessive gluconeogenesis, and impaired glucose use in peripheral tissues are considered to be the driving forces behind stress hyperglycemia in critically ill adults [2,3]. Studies in critically ill children have reported an association between hyperglycemia and morbidity (e.g., longer length of stay [LOS] in the intensive care unit [ICU], duration of ventilator use, and an adverse neurologic outcome) [1].

The underlying mechanisms of hyperglycemia and risk factors in critically ill children have been little studied and only in small groups of patients [4,5]. Van Waardenburg et al. [4] proposed that hyperglycemia associated with hypoinsulinemia rather than insulin resistance may be the normal pathophysiologic response, at least in children with meningococcal septic shock. Preissig and Rigby [5] reported a different etiology of hyperglycemia in critically ill children that is dependent on the presence of respiratory and/or cardiovascular failure. Insulin resistance, as defined by an increased C-peptide/glucose ratio, was the prominent cause of hyperglycemia in children with respiratory failure only versus primary β-cell dysfunction in children with respiratory and cardiovascular failures [5].

Intensive insulin therapy in critically ill children (targeting blood glucose concentrations 2.8–4.4 mmol/L [50–80 mg/dL] in infants and 3.9–5.5 mmol/L [70–100 mg/dL] in older children)

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resulted in shorter ICU LOS and fewer secondary infections [6]. We have successfully implemented a nurse-driven glucose control protocol for critically ill children of all ages with hyperglycemia (defined as blood glucose level >8 mmol/L [>145 mg/dL]) at any time during admission. This resulted in normoglycemia within 12 h for 94% of the children involved without episodes of hypoglycemia (≤2.2 mmol/L) [7].

The focus of our research was to investigate the relations of baseline insulin/glucose ratio to the clinical course of critically ill children. Such information will provide insight into the pathophysiologic mechanisms leading to hyperglycemia and will optimize preventive and therapeutic measures for hyperglycemia in critically ill children.

Better insight into the pathophysiologic mechanisms leading to hyperglycemia will enable the implementation of optimal preventive and therapeutic measures concerning hyperglycemia in critically ill children. We related the endogenous insulin response to hormonal parameters (insulin and cortisol), metabolic parameters (free fatty acids, triacylglycerols, cholesterol, and lactate) and immunologic parameters (C-reactive protein and white blood cell count) just before the start of insulin therapy.

Because insulin therapy increases the risk of hypoglycemia with its adverse effects, it seemed essential to define the categories of critically ill children who might benefit from insulin therapy. Therefore, we also looked at specific laboratory and clinical markers that might predict a beneficial effect from insulin therapy.

Materials and methods

Setting

The pediatric ICU (PICU) of the university children's hospital is a tertiary 34-bed multidisciplinary unit providing for high acute medical and surgical conditions in children up to 18 y old.

Design

This was a prospective evaluation of critically ill children 2 wk to 18 y of age consecutively admitted to the PICU of the Erasmus MC–Sophia Children's Hospital from January 2006 through July 2009 and showing hyperglycemia (defined as blood glucose level >8 mmol/L [>145 mg/dL]) that met the criteria for insulin treatment [7]. Children with diabetes mellitus were excluded. The local medical ethics review board approved the study.

Clinical characteristics and outcome parameters

Patients' baseline characteristics and other clinical information were recorded. Anthropometric measurements were taken on the day of admission.

Disease severity was determined by the Pediatric Risk of Mortality II score and the Pediatric Logistic Organ Dysfunction scoring system [8,9].

Respiratory and inotropic support and the use of glucocorticoids and antimicrobiologic agents were recorded. Inotropic support was quantified by the vasopressor score developed by Hatherill et al. [10]. We calculated equivalent doses of prednisolone, expressed per body weight (milligrams per kilogram), using the glucocorticoid equivalent potencies 20, 5, and 0.75 for hydrocortisone, prednisolone, and dexamethasone, respectively.

Children received standardized analgesia and nutritional support [11]. The glucose-control protocol prescribes glucose intake rates dependent on body weight and an insulin dose dependent on the actual blood glucose level. The actual glucose intake was calculated. All children were on continuous enteral and/or parenteral feeding.

Laboratory tests

A standard-care, physician-initiated, nurse-driven, glucose-control protocol was used to screen and treat all hyperglycemic patients [7]. Blood glucose measurements were obtained as soon as possible after admission. In the case of hyperglycemia (>8 mmol/L [>145 mg/dL]), measurements were repeated every hour and further according to the protocol. Blood was collected from an indwelling arterial or venous catheter or from capillary puncture. Arterial blood samples for the determination of glucose, insulin, cortisol, C-reactive protein, lactate, cholesterol, free fatty acids, triacylglycerols, creatinine, urea, aspartate aminotransferase, alanine aminotransferase, and prothrombin time were taken at the start of insulin therapy. All laboratory parameters were determined immediately in a certified laboratory of clinical chemistry (International Organization for Standardization 17025 and 9001). Assays were performed according to the manufacturers' instructions.

Blood glucose was measured in a blood gas analyzer (ABL 625; Radiometer, Copenhagen, Denmark) or by a bedside capillary glucose measurement with a point-of-care system (HemoCue AB, Ängelholm, Sweden). Blood glucose levels lower than 2.6 mmol/L (<47 mg/dL) or higher than 15 mmol/L (>272 mg/dL) obtained by the latter method were considered unreliable. Measurements were then repeated using the blood gas analyzer. Hypoglycemia was defined as a blood glucose level lower than or equal to 2.2 mmol/L (≤40 mg/dL) and hyperglycemia as a blood glucose level higher than 8.0 mmol/L (>150 mg/dL) [7].

Serum insulin was measured by a two-site chemiluminescent immunometric assay (Immulite 2000; DPC, Los Angeles, CA, USA) with a minimum detection level of 35 pmol/L. The maximum fasting reference value for insulin was set at 180 pmol/L. The insulin/glucose ratio was calculated to assess insulin sensitivity. The maximum reference value for the insulin/glucose ratio was defined as 18 pmol/mmol. This value was derived from current literature data, taking into account the differences between insulin assays and units of analysis [4,12,13]. Insulin sensitivity was also measured using the homeostasis model assessment (HOMA). Scores higher than or equal to 4 indicate decreased insulin sensitivity [14].

Serum cortisol concentrations were determined with a competitive luminescence immunoassay (Immulite 2000). The detection limits of this assay are 3 to 1380 nmol/L. Non-stressed reference values for cortisol were 200 to 800 nmol/L. Although there are no strict definitions on adrenal insufficiency assessment in critically ill children, adrenal insufficiency in the case of catecholamine-resistant septic shock may be assumed at a random level lower than 496 nmol/L [15].

Arterial lactate was determined in a blood gas analyzer (ABL 625). The reference level for lactate was lower than 2.0 mmol/L. Serum C-reactive protein was determined by an immunoturbidimetric assay (normal <2 mg/L) and examined in a 912 analyzer (Roche Molecular Biochemicals, Mannheim, Germany).

Plasma free fatty acid concentrations were determined by an enzymatic method (Nefac-kit, Wako, Instruchemie BV, Delfzijl, The Netherlands). Reference levels for free fatty acids were 0.3 to 1.1 mmol/L for children 4 mo to 10 y old and 0.2 to 0.8 mmol/L for children older than 10 y.

Statistics

Data were analyzed with SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). Results are expressed as median (range), unless specified otherwise. Data were log-transformed when necessary. Mann-Whitney U test was used for group comparison. Chi-square test was used for comparison of nominal data. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The study group consisted of 64 children (24 girls, median age 7.0 y, range 0.3–16.9 y) with various diagnoses. Fifty-one had respiratory or cardiovascular failure, for which they received mechanical ventilation or inotropic support. There were no children with severe hepatic failure. One child was admitted with acute renal insufficiency requiring dialysis therapy. Eleven children (17%) died during PICU admission. Five of them died during insulin therapy. Patients' characteristics just before the start of insulin therapy are presented in Table 1.

Insulinemic response

Blood samples were taken just before the start of insulin treatment. The group median blood glucose level at the start of therapy was 9.9 mmol/L (5.7–43.3 [180 mg/dL, 104–787]). Median plasma insulin level was 235 pmol/L (<35–3803). Insulin levels were below the detection level in three patients. The median insulin/glucose ratio was 20 pmol/mmol (1–235). The median HOMA value was 13 (2–385).