MANAGEMENT OF SEVERE DIABETIC KETOACIDOSIS IN A YOUNG ADULT

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We present a case of severe diabetic ketoacidosis in a 19-year-old male with a history of poor compliance to insulin therapy. At arrival to our Emergency Department, the patient was comatose with extreme hyperglycemia, severe diabetic ketoacidosis, lactic acidosis and dehydration. The treatment consisted of intensive fluid replacement and correction of all metabolic disturbances until complete recovery. In the vast majority of severe diabetic ketoacidosis cases, relatively fast and successful treatment result can be expected if intensive therapy is applied and if ketoacidosis is not triggered by a serious illness. Some essential contemporary guidelines and the importance of individual treatment approach are pointed out in the article. The role of high serum procalcitonin value in diabetic ketoacidosis is discussed.

Key words: diabetic ketoacidosis, hyperosmolar state, hypovolemia, treatment of diabetic ketoacidosis

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INTRODUCTION

Diabetic ketoacidosis (DKA) is most common among patients with type 1 diabetes mellitus (DM) and develops when insulin levels are insufficient to meet the body's basic metabolic requirements. It is characterized by modest or rarely extreme hyperglycemia, hyperketonemia, ketonuria and metabolic acidosis (1). Excessive glucose secretion by kidneys overcomes the glucose tubular maximum reabsorption creating a hyperosmolar state in renal tubules, which causes osmotic diuresis with significant fluid and electrolyte loss. Almost absolute lack of insulin forces the body to metabolize triglycerides and amino acids instead of glucose for energy, which in return results in excessive production of ketones (2). Hyperglycemic nonketotic state is more often seen in type 2 DM where even minimal pancreatic insulin secretion does not allow excessive ketone production (3).

CASE REPORT

A 19-year-old male with a five-year history of poor regulation of DM was admitted to our Intensive Care Unit (ICU) for clinical and laboratory signs of severe DKA, extreme hyperglycemia, hypovolemia, dehydration, hypotension and lactic acidosis. He was found at home unresponsive, tachypneic, with nausea and vomiting, which had lasted for four days until hospital arrival. During that time, there was no liquid or food intake or insulin application. Laboratory tests were as follows: RBC $4.9x10^{12}$/L, Hb 154 g/L, Htc 0.53 L/L, MCV 110.6 fL, L $25.6x10^{9}$/L, platelet count $348x10^{9}$/L, C-reactive protein (CRP) 132.2 mg/L; venous blood gas analysis: pH 6.83, pCO_2 2.3 kPa, BE -30.5 mmol/L, pO_2 11.24 kPa, bicarbonates 2.9 mmol/L, total CO_2 3.4 mmol/L, O_2 saturation 84.7 percent, blood glucose 87.9 mmol/L, creatinine 317 μmol/L, urea 11.8 mmol/L, lactic acid 3.2 mEq/L, AST 48 U/L, ALT 62 U/L,

K 7.2 mmol/L, Na 116 mmol/L, Cl 75 mmol/L, and procalcitonin (PCT) 34.9 ng/mL. Upon arrival to the ICU, the patient was comatose and smelled of acetone, with Kussmaul breathing 27 breaths/min, tachycardia 105/min, hypotension 85/45 mm Hg, oxygen saturation of 86% on pulse oximetry at room air (hypotension!). Glasgow Coma Score was 7 and central venous pressure (CVP) was -4 cm H_20. Urgent chest x-ray was normal. Neurological examination showed slightly delayed reflexes and decreased muscle tone consistent with altered mental status. Electrocardiography was within the normal range. Urine bacteriology, blood and stool cultures were sterile. In order to establish normotension and diuresis to induce glycosuria and ketonuria and to correct lactic acidosis, the patient received 1500 mL of normosaline volume replacement in the first 90 minutes. Normosaline infusions continued up to the total of 7 L in the first 24 hours at the average infusion rate of 245 mL/hour and periodical control of CVP. At the very beginning, the patient received an intravenous bolus of 12 i.u. of rapid acting insulin, which was continued as a rapid acting insulin infusion at the average dose of 12 i.u. *per* hour, and close monitoring of blood glucose level every 2 hours. Total amount of rapid acting insulin applied intravenously in the first 24 hours was 300 i.u. Due to the severely low pH and consecutive high serum potassium, sodium bicarbonate infusion was included in therapy at the rate of 30 mL/hour. In the next five hours, the level of 7.2 and 5.9 mmol/L was reached for pH and potassium, respectively, which allowed bicarbonate therapy to be stopped. However, as blood glucose level and ketoacidosis improved, severe serum depletion of potassium occurred, which required replacement of 400 mL of KCL in the first 48 hours and monitoring of serum potassium level every 6 hours. Following improvement of laboratory parameters, the patient's mental status recovered, and so did his food and water intake *per os*. Insulin therapy was switched to subcutaneous application. After two days of treatment, complete resolution of DKA was reached, the patient was transferred to the Department of Endocrinology and soon discharged from the hospital.

DISCUSSION

Regular clinic attendance is recommended to facilitate self-management of diabetes. Poor attendance is common among young adults with type 1 DM, which precipitates acute diabetic complications (4). Psychosocial factors such as socioeconomic status, parental separation and lack of family cohesiveness, unemployment, psychological and mental health factors including eating disorders and substance abuse play a crucial role in the management of DM in young adults.

The high frequency of DKA in known type 1 DM indicates the need of particular focus on adolescents (5). Spaic *et al.* found that structured transition program for young adults with type 1 diabetes improved clinic attendance, glycemic control, diabetes-related distress, quality of life, and satisfaction with care in regard to standard care (6).

In our patient, history data were not indicative of socioeconomic or family problems, but his compliance was very poor and probably associated with psychological profile.

Hypovolemia induced by osmotic diuresis includes the loss of fluid, sodium and potassium (7). However, serum potassium is usually raised because of ketoacidosis, which is responsible for cell potassium reaching serum. Low serum potassium level at arrival means severe exhaustion of potassium cell backup. Hypovolemia and consecutive hypotension stimulate the release of counter-regulatory diabetogenic hormones such as adrenaline and cortisol, thus causing further increase in serum glucose level. Therefore, immediate volume replacement is of crucial importance and as urgent as the administration of rapid acting insulin (8). Any therapy during hypotension must be applied intravenously. Normosaline infusion is generally the best choice because of the usually low sodium level and high blood glucose level (9).

The optimal rate of isotonic saline infusion depends on the patient's clinical condition. Primary goal is to reach normotension and diuresis as soon as possible. Although the fluid challenge therapy might be a double-edge sword, we found it safe and useful for our young patient in severe hypovolemic state. When replacing the volume, special attention must be paid to older patients or patients with heart or renal insufficiency (10).

Insulin therapy should be initiated with IV bolus of regular insulin (0.1 units/kg body weight), followed by continuous infusion of regular insulin of 0.1 units/kg *per* hour (11). The bolus dose can be omitted if a higher dose of continuous IV regular insulin is initiated (0.14 units/kg *per* hour). Higher doses do not produce a more prominent hypoglycemic effect due to saturation of insulin receptors. In mild DKA, patients can be safely treated with subcutaneous, rapid-acting insulin analogs. There is no difference in treating DKA with IV regular insulin and rapid-acting insulin analogs, along with much lower cost of regular insulin therapy.

When serum glucose in DKA falls to less than 12 mmol/L, but bicarbonate and pH values are not normalized, glucose infusion is recommended (12). Each

500 mL of 5% and 10% glucose infusion must contain 8 and 16 IU of rapid acting insulin, respectively, in order to provide glucose utilization and therefore enough energy to stop ketogenesis.

In patients with euglycemic DKA, both insulin and glucose therapy is necessary, and the response to low-dose insulin therapy improves with adequate rehydration (13).

We strongly advise to synchronize potassium replacement with laboratory monitoring. When potassium level is high, any replacement in advance is not recommended.

Insulin therapy promotes potassium uptake by the cells along with glucose and may trigger cardiac arrhythmias. In severe hypokalemia (below 3.3 mEq/L), potassium administration in 500 mL of normosaline infusion at the rate of 10 to 20 mEq/hour will be sufficient for most patients. It must be followed by serum potassium measurements every two hours and stopped immediately when normal range is reached (14). Patients at risk of volume overload can receive more concentrated potassium infusion *via* central venous catheter at the same dose but at a lower rate *per* hour. The indications for bicarbonate therapy in DKA are controversial and there is not enough evidence for its benefit (15). If arterial pH is 6.9 or less, as in our patient, it might be of certain help, although most authors will cease this therapy as soon as the pH value reaches 7.0. In patients with potentially life-threatening potassium level over 6.4 mEq/L, bicarbonate therapy should be used until the level falls below 6.4 mEq/L (16).

Initially, monitoring involves measurements of serum glucose every hour until the profile becomes relatively stable. Serum electrolytes, creatinine, and venous blood gas analysis should be measured every two to four hours, depending on DKA severity and clinical response (17).

When ketoacidosis is resolved and the patient is ready for oral intake, subcutaneous insulin schedule should be started and IV insulin infusion should be continued for one or two hours after initiating subcutaneous insulin to prevent recurrence of hyperglycemia or ketoacidosis. In patients previously treated with insulin, the established insulin regimen may be restarted.

It is well-established that DKA is associated with leukocytosis and an increase in acute phase proteins, including CRP, tumor necrosis factor alpha, interleukin 1 beta (IL-1β), IL-2, IL-6 and IL-8.2 (18). Moderate increase of serum levels of procalcitonin in DKA is less known but practitioners should be aware that increases in CRP and PCT may occur in patients with DKA in the absence of bacterial infection, thus avoiding unnecessary examinations such as blood cultures and treatments (antibiotics) if other signs of infection are not present (19).

Extremely high value of procalcitonin as in our patient, in the proved absence of bacterial infection is very rare. However, it may be a consequence of synergistic effect of ketoacidosis and extremely high blood glucose level. It has been reported that correction of plasma glucose levels leads to a decrease of PCT concentrations in patients presenting with acute hyperglycemia (20), which is exactly what happened in our patient.

CONCLUSION

Therapeutic approach to DKA should be individual, the patient must receive adequate volume, adequate dose of insulin, appropriate electrolyte replacement, and must be carefully monitored. At the same time, precipitating events or triggers of ketoacidosis such as infection should be intensively looked for. DKA is frequently accompanied by moderate increase of serum levels of CRP and procalcitonin, which does not necessarily reflect the presence of bacterial infection. As a result of actual therapy guidelines, further possible complications of DKA have become less common.

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SAŽETAK

LIJEČENJE TEŠKE DIJABETIČKE KETOACIDOZE U MLADE OSOBE

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Prikazan je slučaj 19-godišnjeg bolesnika od dijabetesa koji nije redovito primjenjivao inzulin. Bolesnik je doveden na naš Objedinjeni hitni prijam u komatoznom stanju, s ekstremnom hiperglikemijom, teškom dijabetičkom ketoacidozom, laktacidozom i dehidracijom. Liječen je intenzivnom nadoknadom volumena i korekcijom svih metaboličkih poremećaja do potpunog oporavka. U velikoj većini slučajeva teških dijabetičkih ketoacidoza može se očekivati relativno brza i uspješna korekcija ako se primijeni intenzivno liječenje i ako ketoacidoza nije potaknuta ozbiljnom bolesti. U članku su navedene neke bitne suvremene smjernice u liječenju i naglašena je važnost individualnog pristupa. Raspravljena je i uloga visoke serumske vrijednosti prokalcitonina u dijabetičkoj ketoacidozi.

Ključne riječi: **dijabetička ketoacidoza, hiperosmolarno stanje, hipovolemija, liječenje dijabetičke ketoacidoze**