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Acute complications of diabetes – the present state of knowledge. Part III. Lactic acidosis

Ostre powikłania cukrzycy – stan wiedzy. Część III. Kwasica mleczanowa

INTRODUCTION

Lactic acidosis (LA) may be responsible for metabolic acidosis due to anoxia or ischaemia, to which patients with diabetes are prone, and is associated with poor prognosis. It has been reported that blood lactate concentration is one of the best predictors of fatal outcome in the critical care units [10]. LA is also a well recognized complication of biguanide therapy which is potentially serious [4]. With the discontinuance of phenformin therapy in the world, LA in patients with diabetes mellitus has become uncommon, but it still must be considered in the acidotic diabetic patient if the patient is seriously ill, and especially if the patient is receiving metformin therapy as well. Although the prevalence of metformin-associated lactic acidosis (MALA) is much lower than that associated with phenformin, it is still being reported. The mortality rate is very high in the course of LA, and there is no satisfactory treatment other than treatment of the underlying cause. LA should be suspected when severely ill diabetic patients present with profound acidosis and an elevated anion gap over 16 mEq/L but relatively low or undetectable levels of ketone bodies in plasma or in urine [16].

EPIDEMIOLOGY

Epidemiological data concerning LA indicate that this complication is the most frequent cause of metabolic acidosis, with a prevalence of 1% among adult hospitalized patients [8]. Lactic acidosis in diabetic patients usually occurs in association with critical illness, such as severe tissue anoxia, sepsis, or cardiovascular collapse, which are more common in diabetic patients than in non-diabetic subjects [5, 8] Lactic acidosis is common in severely ill patients suffering from cardiac decompensation, respiratory or hepatic failure, septicemia, or infarction of the bowel or extremities.

LACTIC ACIDOSIS

D e f i n i t i o n . LA is defined as a high anion gap metabolic acidosis, when anion gap exceeds 16 mEq/L with a blood lactate concentration > 5,0 mmol/L. This pathological elevation of lactic acid may result from overproduction or delayed clearance of lactate, or a combination of both.

P a t h o g e n e s i s . Lactic acid is the end product of the anaerobic metabolism of glucose. Physiologically, the principal sources of this acid are the erythrocytes (which lack the enzymes for aerobic oxidation), skeletal muscle, skin, and brain. Anaerobic glycolysis results in the production of lactate and hydrogen ions, which are extracted by the liver, kidneys, and heart under normal aerobic conditions, and either oxidised completely to carbon dioxide and water, or entered into the gluconeogenic pathway. LA may be classified according to the presence or absence of hypoxia into type A and type B [8]. Type A lactic acidosis, which is anaerobic or hypoxic, occurs in states of tissue hypoxia such as myocardial infarction, cardiogenic shock, or profound sepsis. In this situation, anaerobic metabolism produces excess lactate that can not be removed form the body and clearance of lactate may also be decreased. This situation is not specific to diabetes but patients with diabetes, especially with type 2 diabetes, are at increased risk of hypoxic cardiovascular complications. Type B lactic acidosis, which is called aerobic, is a rare condition and is associated with a number of systemic diseases (including diabetes), drugs, toxins, and inborn errors of metabolism [5]. The biguanides metformin and phenformin, used in the treatment of type 2 diabetes, have both been also associated with the development of type B lactic acidosis [2]. Phenformin was withdrawn from the market because of this complication; the incidence of lactic acidosis is much lower with metformin, with an estimated incidence of 0.03 episodes per 1000 patient years [2]. MALA may be either type A lactic acidosis, where the acidosis is the result of concurrent complicating illness without the accumulation of metformin, type B arising from marked metformin accumulation without concurrent hypoxic factors; or mixed, resulting from a combination of the above factors. Ninety percent of absorbed metformin is excreted unchanged by the kidneys and so it is the renal function that determines metformin clearance [4]. The principal contraindication to using metformin is renal impairment: the American Diabetes Association recommends avoiding metformin use if serum creatinine concentration is elevated [1]. Because of the accumulation of lactate in hypoxia, metformin is also contraindicated in conditions such as uncontrolled heart failure which predisposes to lactic acidosis [13]. Another type of LA was also described called D-Lactic LA, which may be associated with jejunoileal bypass, short bowel syndrome, or intestinal obstruction, and LA is due to the formation of D-lactate by gut bacteria [14].

E t i o l o g y . The main causes of LA type A, which is connected with tissue hypoxia include: shock (e.g., cardiogenic, endotoxic, hypovolaemic, hemorrhagic), cardiac failure, asphyxia, seizures, carbon monoxide or cyanide poisoning. Type B of LA may develop in the course of numerous systemic diseases, such as diabetes, malignancies, liver diseases [5]. Drugs like biguanides, salicylates or toxins such as ethanol, methanol, ethylene glycol are another group of causes. Other possible causes of LA include inborn errors of metabolism: type 1 glycogen storage disease or fructose 1,6-diphosphatase deficiency [12].

C l i n i c a l p i c t u r e . The major clinical symptoms in LA are very non-specific. The main clinical features of LA are marked hyperventilation and mental confusion, which may progress to

stupor or coma. When LA is secondary to tissue hypoxia or vascular collapse, the clinical presentation may be variable, being the result of the prevailing severe illness. Clinical picture includes tachypnoea (which is known as Kussmaul respiration), nausea, vomiting, diarrhoea, epigastric pain, anorexia, lethargy, thirst, and a decreased level of consciousness [11]. Hypotension, hypothermia, cardiac arrhythmias, and respiratory failure may also occur in severe metformin-associated lactic acidosis [6]. Blood glucose levels may be low, normal, or high in diabetic subjects, but usually they are moderately elevated. Plasma bicarbonate and arterial pH are very low. An anion gap is elevated, which may be easily calculated by subtracting the sum of plasma bicarbonate and chloride from the plasma sodium. The normal anion gap is between 8–16 mEq/L. Ketones are usually absent from plasma, but small amounts may be present in urine if the patient has not been eating recently. It is very important that other causes of metabolic acidosis with elevated anion gap should be excluded, e.g., uremia, diabetic or alcoholic ketoacidosis, and salicylate, methanol, ethylene glycol, or paraldehyde intoxication. It should also be emphasized that lactic acidosis may accompany ketoacidosis [8].

D i a g n o s i s . The diagnosis of LA is confirmed by demonstrating, in a sample of blood that is promptly chilled and separated, a plasma lactate concentration of 5 mmol/L or higher (normal concentration of lactic acid is < 1 mmol/L). Failure to rapidly chill the sample and separate the plasma can lead to falsely high plasma lactate values as a result of glycolysis by the red blood cells. Other important features for diagnosis are moderated hyperglycemia, but it should be noticed that glucose concentration in blood serum can be normal, decreased blood pH <7.1, bicarbonate content < 10 mmol/L and an anion gap > 16 mEq/L, normal sodium concentration in extracellular fluid and elevated potassium level as a consequence of severe acidosis [16].

D i f f e r e n t i a l d i a g n o s i s . LA should be differentiated from other diabetic comas, metabolic acidosis (uremic, hepatic), CNS disorders (cerebral stroke, tumours, inflammations), myocardial infarction, thyroid, adrenal, hypercalcemic crises, poisonings (glycol, methanol, salicylates), psychiatric disorders and starvation ketosis.

T r e a t m e n t . It should be emphasized that the cornerstone of therapy is aggressive treatment of the precipitating cause. Treatment of lactic acidosis includes appropriate supportive care (usually carried out on an intensive care unit), treatment of any concomitant condition and elimination of any offending drug by renal excretion or dialysis [5,10,15]. An adequate airway and good oxygenation should be ensured. Glucose infusion and insulin therapy should be administered in order to decrease the production of lactate. Insulin therapy should be conducted using short-action insulin in the form of intravenous infusion with an infusion pump. If hypotension is present, fluids and pressor agents must be given to restore tissue perfusion. Appropriate cultures and empiric antibiotic treatment should be employed. The essential aim of treatment of LA is to control water – electrolyte disturbances and return acid – base balance. Alkalinization with intravenous sodium bicarbonate to keep the pH above 7.2 has been recommended in the emergency treatment of severe lactic acidosis. However, there is no evidence that the mortality rate is favorably affected by administering bicarbonate, although bicarbonate therapy is still one of the principal managements for lactic acidosis despite conflicting reports [7]. It has been reported that drugs used to treat lactic acidosis can even aggravate the condition [10]. It has been documented that bicarbonate increases lactate production. Treatment of type A lactic acidosis is particularly unsatisfactory and administration of bicarbonate is of little

value. A new hope was connected with Carbicarb, that is a mixture of Na_2CO_3 and $NaHCO_3$ that buffers similarly to $NaHCO_3$ but without net generation of CO_2 [3]. The initial results from animal studies were promising; however, more clinical trials are needed. Another agent for treatment of LA, dichloroacetate, an anion that facilitates pyruvate removal by activating pyruvate dehydrogenase, reverses certain types of lactic acidosis in animals and improves laboratory values, but unfortunately in a prospective controlled clinical trial involving 252 patients with lactic acidosis, this agent failed to alter either hemodynamics or survival rates [12]. Hemofiltration has been advised for the treatment of lactic acidosis, on the basis of anecdotal experiences, but not evidence based medicine [9]. However, kinetic studies of lactate removal do not suggest that removal can counteract lactate production. Hemodialysis may be useful in those cases in which metformin accumulation and the attendant lactic acidosis occurred in patients with renal insufficiency. Metformin is a dialysable drug and the use of bicarbonate in combination with haemodialysis has been successful in the management of metformin associated lactic acidosis [4].

In summary, general management of the underlying condition, appropriate supportive care, bicarbonate therapy and haemodialysis are the key approaches to the management of severe lactic acidosis. On the basis of the current state of knowledge it can be concluded that the ideal treatment is to stop acid production by treating the underlying disorder.

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SUMMARY

Nowadays, lactic acidosis (LA) is a rather rare acute hyperglycemic diabetic complication, which complicates the course of the disease and increases the mortality rate. The most frequent cause of developing LA in patients with diabetes is tissue anoxia or ischaemia, to which patients with diabetes are extremely prone. The course of LA is still associated with poor prognosis and increased blood lactate concentration is one of the best predictors of the fatal outcome in the critical care units. LA is also a well recognized complication of biguanide therapy in patients with type 2 diabetes. The basis for diagnosis is severe metabolic acidosis with elevated anion gap exceeding 16 mEq/L with a blood lactate concentration > 5.0 mmol/L. The study presents the current state of knowledge about LA concerning epidemiology, pathogenesis, clinical picture and particularly current standards of treatment.

Keywords: lactic acidosis, diabetes, epidemiology, pathogenesis, clinical picture, standards of treatment

STRESZCZENIE

Kwasica mleczanowa to obecnie dość rzadko występujące ostre, hiperglikemiczne powikłanie cukrzycy, które komplikuje przebieg choroby i zwiększa śmiertelność. Najczęstszą przyczyną wystąpienia kwasicy mleczanowej u chorych na cukrzycę jest niedotlenienie tkanek, na które pacjenci z cukrzycą są niezwykle podatni. LA charakteryzuje złe rokowanie, a zwiększone stężenie mleczanu we krwi jest jednym z największych predyktorów śmiertelności w oddziałach intensywnej terapii. Ciężka LA jest również związana z terapią biguanidami u chorych z cukrzycą typu 2. Podstawą rozpoznania jest stwierdzenie ciężkiej kwasicy metabolicznej z podwyzszona luką anionową przekraczającą 16 mEq/L oraz stężeniem mleczanu we krwi > 5 mmol/L. Praca przedstawia stan wiedzy na temat kwasicy mleczanowej w zakresie epidemiologii, patogenezy, obrazu klinicznego, a szczególnie bieżących standardów leczenia.

Słowa kluczowe: kwasica mleczanowa, cukrzyca, epidemiologia, patogeneza, obraz kliniczny, standardy leczenia