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Лактацидоз при остром повреждении почек и терапии метформином

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В статье приведено клиническое наблюдение развития редкого патологического состояния — лактацидоза у пациентки с острым повреждением почек на фоне приема метформина, и подтверждена необходимость своевременного определения лактата крови.

Клинический случай подтверждает, что развитие лактацидоза у пациента с сахарным диабетом может иметь смешанную этиологию и связано не только с приемом метформина, но и наличием тканевой гипоксии, воздействием инфекционного процесса, нарушением функции почек.

Развитие лактацидоза связано с повышением секреции и/или уменьшением скорости выведения лактата, что выражается в состоянии метаболического ацидоза и тяжелой сердечно-сосудистой недостаточности. Его также часто связывают с наличием почечной и/или печеночной недостаточности, сахарного диабета, патологии легких, нарушений макро-/микроциркуляции, дефектов функций гемоглобина и лечением препаратами бигуанидов (метформином). Диагностика лактацидоза основывается на данных биохимического анализа крови и электролитных показателях — концентрации лактата плазмы крови, исследовании кислотно-основного состояния крови и анионного интервала.

Ключевые слова: лактацидоз; метформин; сахарный диабет; острое повреждение почек.

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Case of lactacidosis in acute kidney damage and metformin therapy

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The article provides a clinical observation of the development of a rare pathological condition of lactic acidosis in a patient with acute kidney injury while taking metformin and confirms the need for timely determination of blood lactate.

The clinical case confirms that the development of lactic acidosis in a patient with diabetes mellitus may have a mixed etiology and be associated not only with the use of metformin, but also with the presence of tissue hypoxia, exposure to an infectious process, and impaired renal function.

The development of lactic acidosis is associated with an increase in secretion and / or a decrease in the rate of excretion of lactate, which is expressed in a state of metabolic acidosis and severe cardiovascular insufficiency. The development of lactic acidosis is most often associated with the presence of renal and / or hepatic insufficiency, diabetes mellitus, lung pathology, macromicrocirculation disorders, and hemoglobin function defects, the treatment with biguanide drugs (metformin). Diagnosis of lactic acidosis is based on the data from a biochemical blood test and electrolyte parameters – the concentration of blood plasma lactate, the study of acid-base state of the blood and anion gap.

Keywords: lactic acidosis; metformin; diabetes mellitus; acute kidney injury.

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BACKGROUND

Lactic acidosis (lactacidosis) is a pathological condition of increased production and/or decreased clearance of lactate, as manifested by severe cardiovascular insufficiency with severe metabolic acidosis. Currently, lactic acidosis in diabetic patients is relatively rare, and its annual incidence in different countries ranges from 0.027 to 0.053 cases per 1000 patients. Mortality in lactic acidosis reaches 50%–90%, and it often develops rapidly with only a few hours from the first symptoms to the terminal state. Various causes of lactic acidosis are directly related to hypoxia of various etiologies, which causes the activation of anaerobic glycolysis with an excess of lactate. The etiological factors for the occurrence of hypoxia include severe infectious and inflammatory processes in diabetes mellitus, respiratory and cardiovascular insufficiency, anemia, renal and hepatic insufficiency, and the intake of drugs and toxic substances. In particular, lactic acidosis pathogenesis caused by biguanide intake is based on the activation of the anaerobic glycolysis process in the small intestine and the muscular system, due to which lactic acid synthesis exceeds glycogen synthesis by the liver. Thus, in the presence of the above causative factors, biguanide intake, even at a therapeutic dose, can provoke the development of lactic acidosis.

The work aimed to analyze a clinical case of detection and treatment of lactic acidosis that occurred in the presence of acute kidney injury and the intake of a therapeutic dose of metformin.

MATERIALS AND METHODS

Case history of a female patient, analysis of Russian and international literature.

EXAMINATION RESULTS

Female patient Sh., 62 years old, was admitted on July 20, 2021, to the intensive care unit (ICU) of the Saint-Petersburg I.I. Dzhanelidze Research Institute of Emergency Medicine with complaints of severe weakness, myalgia in intercostal muscles during breathing, nausea, and decreased diuresis. She had considered herself ill since July 13, 2021, when she was taken to City Hospital No. 26 and discharged before the scheduled date at her own request with a urethral catheter installed and a diagnosis of chronic cystitis, exacerbation, and acute urinary retention.

She had a history of type 2 diabetes mellitus, continuous therapy with metformin 850 mg twice daily (morning and evening), and an absence of diabetic nephropathy. Postoperative hypothyroidism during therapy with levothyroxine 50 μg/day, the condition after left-sided thyroidectomy due to follicular adenoma, the level of thyroid-stimulating hormone at this dose of levothyroxine, according to the patient, was normal (according to regular monitoring by an endocrinologist). After discharge from the city hospital, the patient continued to take metformin of her own accord at the above dosage. She had hypertensive disease stage II (constant intake of enalapril 10 mg/day) and chronic pyelonephritis. The patient denied having had other diseases and taking additional drugs.

Somatic status

The examination revealed a severe general condition of the patient. Consciousness was clear, with 15 points on the Glasgow scale. Qualitative disorders included lethargy and adynamism. Pupils were D = S with brisk photoreaction. Skin integument was of physiological coloring. She had no edema, striae, or hirsutism. The patient was overweight (body mass index 28 kg/m^2), with a gynoid type of subcutaneous fat distribution. There was no smell of acetone in the exhaled air. Body temperature was 37.4°C, blood pressure was 80/50 mmHg, and heart rate was 90/min, with sinus rhythm. Breathing was spontaneous, with breath sounds heard throughout all lung fields, without rales. The respiratory rate was 22/min; blood oxygen saturation was 99%. The abdomen was soft and nontender in all areas. Urination was through the urethral catheter, with a reduced rate of diuresis.

The patient underwent urgent blood and urine tests, electrocardiography, ultrasound examination of the abdominal cavity and kidneys, X-ray of the lungs, and a smear from the throat and nasopharynx to determine the presence of a new coronavirus infection by polymerase chain reaction (PCR). Consultations with a urologist, endocrinologist, cardiologist, septologist, and clinical pharmacologist were prescribed. The patient's test results during admission are presented in Tables 1 and 2.

The PCR test result for the presence of a new coronavirus infection was negative. According to the ultrasound examination of the abdominal cavity and retroperitoneal space, signs of chronic pancreatitis, chronic pyelonephritis, and fatty infiltration of the liver were diagnosed. According to the X-ray of the chest organs, the visible parts of the lungs had no focal and infiltrative changes. According to the electrocardiogram, sinus tachycardia of 105 bpm was detected as well as complete right bundle branch block, left ventricular hypertrophy, and fibrous changes in the myocardium of the lower wall of the left ventricle.

Expert opinions

Examination by a urologist established chronic pyelonephritis, ascending uroinfection, and acute kidney injury.

Examination by a septologist revealed no convincing evidence for the presence of severe sepsis at the time of examination. The condition severity was due to uroinfection associated with acute urinary retention, uremia, hypovolemia, and water and electrolyte disorders.

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Tablel 1. Blood test results during the patient's admission to the hospital

Таблица 1. Результат анализа крови пациентки на момент поступления в стационар

Indicators	Results	Normal
Acidity (pH; artery)	6.819	7.35–7.45
BE ect (artery), mmol/L	–32.4	
BE b (artery), mmol/L	–30.8	
Hematocrit (artery), %	36.7	35–50
Lactate, mmol/L	22.43	0.5–2.2
pO_2 (artery), mmHg	132.2	85–105
Na^+ (artery), mmol/L	130.6	135–148
K^+ (artery), mmol/L	5.98	3–4
pCO_2 (artery), mmHg	11.1	36–45
HCO_3^- (artery), mmol/L	1.8	22–26
Cl^- (artery), mmol/L	90.5	98–107
Anion interval, mEq/L	38.3	<16
Blood osmolarity, mOsmol/L	261	285–295
Erythrocyte sedimentation rate, mm/h	32	2–15
Hemoglobin, g/L	117	120–140
Erythrocytes. $\times 10^{12}$/L	3.9	3.9–4.7
Platelets, $\times 10^9$/L	389	180–320
Leukocytes, $\times 10^9$/L	18.87	4–9
Immature granulocytes, %	5.6	<0.3
Immature granulocytes, $\times 10^9$/L	1.05	<0.03
Neutrophils, $\times 10^9$/L	13.25	1.88–6.48
Basophils, %	0.3	<1
Lymphocytes, %	24	19–37
Monocytes, %	9	3–1
Neutrophils, %	70.2	47–72
Segmented, %	60	47–72
Eosinophils, %	0.5	0.5–5
Stab, %	7	1–6
Urea, mmol/L	26.9	<8.3
Creatinine, μmol/L	880	60–120
Glucose, mmol/L	7.41	3.05–6.38
Total bilirubin, μmol/L	5.8	<21
Total protein, g/L	54.1	64–83
Glycosylated hemoglobin, %	5.9	4.8–5.99

Table 2. Clinical urinalysis results during the patient's admission to the hospital

Таблица 2. Результат общего анализа мочи пациентки на момент поступления в стационар

Indicators	Results	Normal
Relative density, g/L	1013	1008–1025
Transparency	Cloudy	
Color	Orange	
Bilirubin, μmol/L	Negative	<20
Glucose, mmol/L	Normal	<1.7
Ketone bodies, mol/L	Negative	<5
Acidity (pH)	6	4.8–7.4
Urobilinogen, μmol/L	Normal	<70
Protein, g/L	5	<0.1
Leukocytes, $\times 10^2$/μL	5	<0.25
Erythrocytes, $\times 10^2$/μL	2.5	<0.1

Examination by an efferentology specialist established a dehydration syndrome with a full-scale clinical and laboratory presentation, azotemia, and a reduced rate of diuresis as a manifestation of the underlying syndrome. The addition of therapy using dialysis-filtration methods was advisable, provided that azotemia and electrolyte disorders persisted and increased in the absence of fluid deficiency and hemodynamic stabilization.

Examination by a cardiologist revealed no convincing data for the presence of acute focal pathology.

Examination by an endocrinologist established type 2 diabetes mellitus (target glycosylated hemoglobin <7.5%), lactic acidosis associated with acute kidney injury, and metformin intake. An additional examination for the complications of diabetes mellitus was required. Conditions after left-sided hemithyroidectomy for follicular adenoma and postoperative hypothyroidism on hormone replacement therapy (HRT) with levothyroxine were detected.

DISCUSSION OF THE RESULTS

A 62-year-old female patient with a history of type 2 diabetes mellitus, mild anemia, chronic pyelonephritis during medium doses of metformin therapy, and an installed urethral catheter had asthenia, myalgia in intercostal muscles during breathing, a decrease in diuresis, nausea, dyspnea, hypotension, and subfebrile body temperature. The examination revealed a pronounced impairment of the acid-base state in the direction of metabolic acidosis with significant hyperlactatemia (22.43 mmol/L) and an increase in the anion gap to 38.3 mEq/L, confirming the presence of lactic acidosis. The absence of acetone breath odor and hypoketonuria ruled out diabetic ketoacidosis. Due to the development of renal failure and, as a result, a disability of renal tubules to reabsorb, hypochloremia and hyponatremia were noted in blood tests. Hypovolemic hyponatremia contributed to a decrease not only in blood volume but also in serum osmolality, as shown by the patient's tests upon admission. Due to acute kidney injury, a urinalysis showed massive proteinuria, which was reflected by hypoproteinemia. The blockade of adrenergic receptors of the cardiovascular system that develops with hyperlactatemia and the inhibition of chronotropic and constrictive effects of catecholamines contribute to the further development of shock.

Upon admission to the ICU, the following assistance was immediately provided to the patient:

- A central venous catheter was installed.
- Infusion therapy with short-acting insulin in small doses in combination with the administration of glucose under hourly glycemic control was started.
- Taking into account a significant decrease in blood acidity to 6.819, a 4% sodium bicarbonate solution was administered at a dose of 100 mL once intravenously by slow drip.
- The water-electrolyte balance was corrected.
- Antibiotic therapy was performed in agreement with the clinical pharmacologist (ciprofloxacin 800 mg/day and doxycycline 200 mg/day).
- Gastroprotection, thromboprophylaxis with pneumocompression and anticoagulant therapy (Clexane), diuretic (Lasix) and neurometabolic (Cytoflafin) therapy, and HRT for postoperative hypothyroidism (levothyroxine sodium 50 μg/day) were performed.
- Care measures were performed as well as case follow-up by the specialists and control of laboratory tests.

The therapy contributed to a gradual increase and then normalization of diuresis in accordance with the water load. During treatment, myalgias disappeared, and creatinine, urea, and lactate levels and acid-base state of the blood and urine parameters returned to normal. In the absence of the development of azotemia and electrolyte disorders during replenishment of fluid deficiency and stabilization of hemodynamics, the therapy was not supplemented with dialysis-filtration methods. The daily glycemia level at the time of stay in the ICU was 5.7–12.2 mmol/L, and it was 4.7–6.2 mmol/L in the somatic department while following diet No. 9 without hypoglycemic therapy. The total duration of the patient's hospitalization was 15 days, and she stayed in the ICU for 10 days.

At the time of discharge, the patient's condition was satisfactory. The consciousness was clear, and the patient was in contact. There was no acetone odor in the exhaled air. Pupils were D = S, of medium size, with photoreaction preserved. The skin was of normal color and moisture. Pulse was 88/min, symmetrical, and regular. The blood pressure was 120/88 mmHg. Heart tones were clear and distinct. Vesicular breath sounds were heard throughout all lung fields, and the respiratory rate was 18/min, with no rales. The abdomen was soft, without bloating, painless on palpation. The liver did not protrude below the costal margin along the midclavicular line on the right. Diuresis was not impaired. In the blood tests, leukocytes were 4.75×10^9/L, creatinine was 103 μmol/L, urea was 5.2 mmol/L, potassium was 3.83 mmol/L, sodium was 145 mmol/L, lactate was 2.0 mmol/L, and thyroid-stimulating hormone was 1.29 μIU/mL. The patient was discharged in a satisfactory condition under the follow-up by a nephrologist, endocrinologist, and cardiologist and received the necessary recommendations.

CONCLUSION

The clinical case confirmed that the development of lactic acidosis in a patient with diabetes mellitus could have a mixed etiology and be associated not only with metformin use but also with tissue hypoxia, exposure to an infectious process, and impaired renal function. At the same time, the use of even therapeutic doses of metformin can increase

metabolic disorders and accelerate the development of lactic acidosis. Thus, with symptoms such as myalgia, hypotension, and oliguria, especially while taking metformin, the blood lactate level should be determined.

Treatment of lactic acidosis as a life-threatening condition is performed strictly in the ICU. It aims to remove lactate and metformin from the body and combat acidosis, hypoxia, and electrolyte disorders. Absolute indications for hemodialysis using a lactate-free buffer are an acidity level of <7.0 and a lactate level of >90 mmol/L. According to the literature, such therapy saves the lives of ~60% of patients with lactic acidosis. To prevent the development of lactic acidosis, it is necessary to cancel timely metformin in patients with the above provoking factors.

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REFERENCES

1. Alfonsova EV. Variation of the some parameters of hemostatic system at the lactat acidosis. *Fundamental research.* 2013;(5–2):240–244. (In Russ.)

2. Alfonsova EV, Zabrodina LA. Role of acidosis in the mechanisms of formation of multiple organ failure (MOF). *Scholarly Notes of Transbaikal State University.* 2014;(1(54)):82–88. (In Russ.)

3. Dedov II, Shestakova MV, Mayorov Yu, et al. Standards of specialized diabetes care. 9th ed. *Diabetes Mellitus.* 2019;22(S1):1–144. DOI: 10.14341/DM221S1

4. Zhukova LA, Sumin SA, Lebedev TYu, et al. Neotlozhnaya endokrinologiya: uchebnoe posobie. Moscow; 2006. P. 35–38. (In Russ.)

5. Potemkin VV. Endokrinologiya. Rukovodstvo dlya vrachey. Moscow: MIA; 2013. (In Russ.)

6. Skvortsov VV, Skvortsova EM, Bangarov RYu. Lactic acidosis in the practice of a resuscitator. *Messenger of Anesthesiology and Resuscitation.* 2020;17(3):95–100. (In Russ.). DOI: 10.21292/2078-5658-2020-17-3-95-100

СПИСОК ЛИТЕРАТУРЫ

7. Альфонсова Е.В. Изменение некоторых показателей системы гемостаза при лактат-ацидозе // Фундаментальные исследования. 2013. № 5–2. С. 240–244.

8. Альфонсова Е.В., Забродина Л.А. Роль ацидоза в механизмах формирования полиорганной недостаточности // Ученые записки Забайкальского государственного университета. 2014. № 1(54). С. 82–88.

9. Дедов И.И., Шестакова М.В., Майоров А.Ю. и др. Алгоритмы специализированной медицинской помощи больным сахарным диабетом. 9-й выпуск // Сахарный диабет. 2019. Т. 22, № S1. С. 1–144. DOI: 10.14341/DM221S1

10. Жукова Л.А., Сумин С.А., Лебедев Т.Ю. и др. Неотложная эндокринология: учебное пособие. М., 2006. С. 35–38.

11. Потемкин В.В. Эндокринология: руководство для врачей. М.: МИА, 2013.

12. Скворцов В.В., Скворцова Е.М., Бангаров Р.Ю. Лактат-ацидоз в практике врача — анестезиолога-реаниматолога // Вестник анестезиологии и реаниматологии. Том 17, № 3. С. 95–100. DOI: 10.21292/2078-5658-2020-17-3-95-100

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