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LACTIC ACIDOSIS AND HIV THERAPY

JAYA A GEORGE, *BM BCh, DTM & H, MSc Immunology, FC Path Clin Path (SA)*
Principal Pathologist, *Department of Chemical Pathology, NHLS Johannesburg Hospital and University of the Witwatersrand, Johannesburg*

LOUISA MKHABELA, *MB ChB*
Medical Officer, *Department of Health, Johannesburg Hospital*

JUNE FABIAN, *FCP (SA)*
Specialist, *Division of Nephrology, Department of Medicine, University of the Witwatersrand, Johannesburg*

Hyperlactataemia, which may result from treatment with nucleoside reverse transcriptase inhibitors (NRTIs), is a spectrum of abnormalities ranging from an asymptomatic condition with hyperlactataemia to a state of metabolic acidosis with blood lactate levels above 5 mmol/l and hepatic steatosis, resulting in high mortality. In this article we briefly review the pathogenesis, clinical features and management of this condition.

Background

NRTIs are nucleoside analogues that prevent DNA elongation and viral reproduction. These drugs are triphosphorylated to become nucleotides and then incorporated into the viral DNA chain by viral reverse transcriptase. Their presence in the DNA halts transcription. They also function as substrates for other enzymes capable of DNA formation, including human DNA polymerase γ, the only enzyme involved in the replication of mitochondrial DNA. Several adverse effects of NRTIs are attributed to mitochondrial damage, including hepatic steatosis and lactic acidosis.

In South Africa the recommended commencement therapy for treatment-naïve patients are two NRTIs, i.e. stavudine (d4T) and lamivudine, and a non-nucleoside reverse transcriptase inhibitor, either efavirenz or nevirapine.

Risk factors

The following is a list of identified risk factors:

- d4T therapy (the most frequently identified risk factor)
- a combination of didanosine (ddI) plus d4T treatment (confers the highest risk)
- female
- obesity
- pre-existing liver disease
- pregnancy
- age (lactic acidosis appears to be rare in children).

Clinical presentation

The presentation varies from an asymptomatic form without acidosis to a severe life threatening lactic acidosis with significant metabolic acidosis. Most patients who test positive for increased lactate levels will be asymptomatic, with mildly elevated lactate levels (< 5 mmol/l) and without an acidosis.

In another group of patients lactate levels may be higher (> 5 mmol/l). These patients are symptomatic, but they do not have a metabolic acidosis. As clinical manifestations are often nonspecific, physicians should maintain a high index of suspicion in patients receiving NRTIs, particularly stavudine. Weight loss is often the first warning sign. Symptoms are gastrointestinal (nausea, abdominal pain and vomiting), weakness, myalgias and tachypnoea.

A third group present with lactate levels > 5 mmol/l as well as a metabolic acidosis. In these patients the prognosis is grave. They deteriorate rapidly, with the development of multi-organ failure. Concurrent conditions include pancreatitis and peripheral neuropathy.

Management

The diagnosis of severe lactic acidosis resulting from NRTI use is one of exclusion. Conditions such as sepsis, pancreatitis, diabetic ketoacidosis and severe hypoxia should be excluded in the initial investigations.

The most important aspects of management are a high index of suspicion and prompt withdrawal of all NRTIs. In cases of lactic acidosis, i.e. lactate >10 mmol/l, or elevated lactate accompanied by significant metabolic acidosis (standard bicarbonate < 15 mmol/l), it is recommended that intravenous fluids be administered together with intravenous thiamine. Admission to an ICU with ventilatory, dialytic and inotropic support may be required. Sodium bicarbonate therapy should be considered in cases of profound acidosis.

After discontinuation of treatment it can take several months for lactate levels to normalise. Uncontrolled data suggest a low rate of recurrence as long as the culprit NRTI is replaced with a non-NRTI or one less frequently associated with hyperlactataemia.

The management of mild (< 5 mmol/l), asymptomatic hyperlactataemia is less certain. Artefactual causes of hyperlactataemia should be excluded. These include exercise before phlebotomy, prolonged application of a tourniquet, failure to use a fluoride oxalate containing tube and delays in labora-

tory analysis. Once these have been excluded one can continue therapy cautiously while monitoring the patient closely for the development of symptoms or further increases in lactate levels. For details refer to the guidelines by the South African HIV Clinicians Society.

Screening

The use of serum lactate for screening has poor positive predictive value for the future development of symptomatic lactic acidosis. Serum lactate levels may be normal in the weeks preceding the development of lactic acidosis. The two mainstays of prevention are patient education and physician vigilance. Simultaneous use of ddI and d4T in the same regimen should be avoided. Patients on d4T, ddI or zidovudine (AZT), the NRTIs most frequently associated with symptomatic lactic acidosis, should be educated regarding its clinical presentation and should seek medical attention immediately should such problems arise. In addition, they should be encouraged to note their weight at each clinic visit and alert the doctor to any unexplained weight loss. Physicians should pay particular attention to unexplained weight loss with or without gastrointestinal symptoms. Investigations of suspected cases should include serum lactate, electrolytes, liver function and serum amylase and lipase. Serum glucose and urea and electrolytes should be analysed to exclude diabetic ketoacidosis.

Conclusions

Hyperlactataemia complicating antiretroviral therapy may be sub-clinical or symptomatic. Symptomatic hyperlactataemia with NRTI use can progress rapidly to liver failure and death and mandates prompt medical intervention.

Further reading

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INTERPRETATION OF BIOCHEMICAL LIVER FUNCTION TESTS

ANNALISE ZEMLIN, *MB ChB, FCPath (SA) Chem, MMed (Chem Path)*
Chemical Pathologist, *Department of Chemical Pathology, NHLS, Tygerberg Hospital and Green Point, Cape Town*

CAREL MEYER, *MB ChB, MMed (Chem Path)*
Chemical Pathologist, *Department of Chemical Pathology, NHLS, Tygerberg Hospital*

The liver weighs 1.2 - 1.5 kg and is the largest organ in the body. It plays a major role in protein, carbohydrate and lipid metabolism. It is also an important site for detoxification, excretion of metabolic end products, storage of iron and synthesis of compounds. It has a large reserve, and generally metabolic disturbances only occur with advanced disease.

Biochemical liver function tests are some of the most frequently requested tests in the clinical setting. These are not only important to establish liver disease, but can also be used to diagnose other conditions not related to the liver. Transient, asymptomatic increases in liver function test values, especially of the transaminase enzymes, are common.

Although tests for clotting time, urea, total protein electrophoresis, ammonia, alpha$_1$-antitrypsin, alpha fetoprotein, ferritin and hepatitis markers are all, part of the evaluation of liver function, their discussion is beyond the scope of this article. Only biochemical tests for the following will be discussed: albumin, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP) and lactate dehydrogenase (LD).

Albumin is the most abundant protein in plasma (30 - 55 g/l). It is an important carrier protein, a contributor to plasma oncotic pressure and an indicator of nutritional status. As albumin is synthesised in the liver, its levels decrease with advanced liver disease. Because of the liver's large reserve capacity, albumin decreases only in the advanced stages of liver disease. Because of its long half-life (19 - 21 days), it does not reflect acute changes in liver synthesising ability.

Bilirubin is a metabolic breakdown product of haem, which is derived from senescent erythrocytes in the reticulo-endothelial system. This unconjugated bilirubin (UB) is bound to albumin. It then enters the liver, where it is modified to an excretable conjugated form (CB) that enters the intestinal lumen via bile. Bacteria can deconjugate this to form urobilinogen (UBG), which is water soluble and may appear in the urine. It is reabsorbed into the circulation (enterohepatic circulation). The albumin-bound UB is not normally found in the urine, as albumin renders the molecule too large for glomerular filtration. The presence of bilirubin in the urine therefore indicates a conjugated bilirubinaemia.

ALT is found in high concentrations in the cytoplasm of hepatocytes. It is also found in very low concentrations in the kidney, heart, skeletal muscle and pancreas. It is significantly raised in hepatocellular damage, such as viral or toxic hepatitis, and only moderately raised in cholestatic jaundice, infectious mononucleosis and liver congestion secondary to congestive cardiac failure or cirrhosis. ALT is more liver specific than AST.

AST is found in the cytoplasm and mitochondria of the hepatocytes, heart, skeletal muscle, pancreas, erythrocytes

and spleen. This enzyme is released from the mitochondria as well as the cytoplasm, and is therefore indicative of more severe cellular damage than ALT. It is increased mainly in hepatocellular damage, such as viral or toxic hepatitis, and also in other conditions such as myocardial infarction, myocarditis, skeletal muscle damage and haemolysis. An AST:ALT ratio of at least 2:1 is suggestive of alcohol abuse.

ALP is found in the liver, in the cells lining the biliary canaliculi, in bone, in the intestine, kidneys and placenta. It is raised in cases of cholestasis and space-occupying lesions of the liver. Because of its numerous sources, it is not liver specific and may also be raised in pregnancy and in bone disease, and there may be a physiological increase in children. Although the liver and bone iso-enzymes may be differentiated by heat inactivation, it is not routinely performed. Specimens should be collected in red-top tubes and not in EDTA-containing purple-top tubes. EDTA can form complexes with the magnesium and zinc needed to catalyse the enzyme reaction, decreasing test result values.

GGT is found predominantly in the liver, but also in the kidney, pancreas and prostate. It is a more specific marker than ALP for cholestatic liver disease and space-occupying lesions. Alcohol and certain drugs such as phenytoin also induce GGT and it is traditionally used in the follow-up of patients who abuse alcohol.

LD is most probably the least unreliable and nonspecific enzyme of the liver function test profile, and therefore some laboratories do not include it. Five LD iso-enzymes have been described and are found in the liver, cardiac muscle, kidney and erythrocytes. Increased levels of LD do not only occur in hepatocellular disease but have been found in numerous other conditions, including myocardial infarction (one of the original cardiac marker enzymes), myocarditis, circulatory failure, skeletal muscle disorders, haematological disorders, malignancies, pulmonary emboli, renal disease and hypothyroidism.

The appropriate use and interpretation of a liver function test plays an important role in the diagnosis and clinical management of a patient. The interpretation of the more liver-specific tests, e.g. bilirubin, ALT and GGT, is helpful in the diagnosis of liver disease, whereas the other results may contribute to compiling the differential diagnosis.

Fig. 1 provides a guide to the interpretation of biochemical liver function tests.

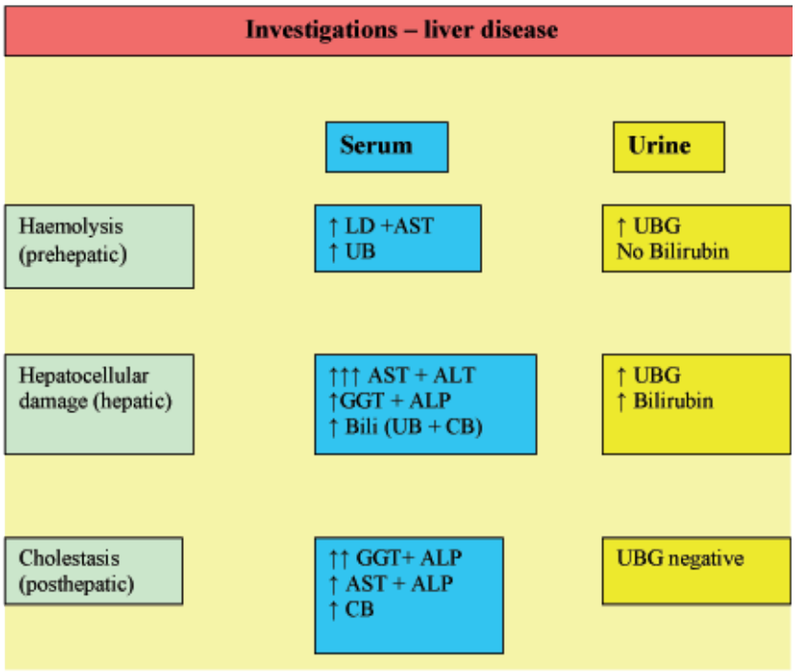

Fig.1. Urine and serum abnormalities of liver function tests in various conditions. LD = lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = glutamyltransferase; ALP = alkaline phosphatase; CB = conjugated bilirubin; UB = unconjugated bilirubin; UBG = urobilinogen.

Further reading

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