Severe drug-induced liver injury associated with prolonged use of linezolid

L De Bus[1], P De Puydt[1,2], L Libbrecht[3], L. Vandekerckhove[4], J. Nollet[1], D Benoit[1], D. Vogelaers[4], H. Van Vlierberghe[5]

[1] Department of Intensive Care, University Hospital, Ghent, Belgium
[2] Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium
[3] Department of Anatomopathology, University Hospital, Ghent, Belgium
[4] Department of Infectious Diseases, University Hospital, Ghent, Belgium
[5] Department of Hepatology, University Hospital, Ghent, Belgium

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Abstract

Objective: To describe a patient developing concomitant severe liver failure and lactic acidosis after long-term treatment with linezolid.

Case Summary: A 55-year old Caucasian woman developed concomitant severe liver failure and lactic acidosis after a treatment with linezolid for 50 days because of infected hip prosthesis. Other causes of liver failure and lactic acidosis were excluded by extensive diagnostic work-up. A liver biopsy showed microvesicular steatosis. As linezolid toxicity was considered to be the cause of the lactic acidosis and the severe hepatic failure, the antibiotic was withdrawn. After four days of supportive therapy and hemodialysis, the serum lactate level returned within normal limits. The prothrombin time and thrombocytes recovered within two weeks. Bilirubin levels normalized within 14 weeks.

Discussion: Since no other cause could be identified, liver injury was considered to be drug related. Resolution of the hepatotoxicity occurred after discontinuation of linezolid, supportive treatment measures and hemodialysis. Both lactic acidosis after the use of linezolid and microvesicular steatosis are related to mitochondrial dysfunction. The Council for International Organizations of Medical Sciences/Roussel Ucalf Causality Assessment Method scale, revealed that the adverse drug event was probable.

Conclusion: Prolonged exposure to linezolid may induce severe hepatotoxicity. Clinicians should be aware of this possible adverse effect especially in case of long-term treatment.

Introduction

Infection of prosthetic devices is frequently caused by Gram-positive pathogens and requires prolonged antibiotic treatment in order to achieve microbial eradication. When methicillin-resistant staphylococci are involved, linezolid is a recommendable therapeutic option as it shows excellent activity against these pathogens and as it has a 100% oral bioavailability.[1] As such, it can be administered orally and on an outpatient basis, whereas treatment with glycopeptides requires intravenous access, which often implies prolonged hospitalization.

Serious side effects of linezolid therapy have been described, including bone marrow toxicity, peripheral and optic neuropathy, and lactic acidosis.[2,3,4] Lactic acidosis has been reported almost exclusively in patients treated for longer than the maximum recommended duration of 28 days. In this report we describe a case of severe drug-induced liver injury (DILI) related to the use of linezolid.

Case Report

A 55-year old woman with rheumatoid arthritis was hospitalized for malnutrition and chronic infection in a prosthetic hip. Upon admission alkaline phosphatase and gamma-glutamyltransferase levels were elevated respectively 4 and 6 times the upper limit values. The hip prosthesis was removed a few days later and oxacillin was started. Transient elevation in transaminases, alkaline phosphatase and gamma-glutamyltransferase (without increase in bilirubin) prompted a diagnostic work-up for liver disease. On abdominal ultrasound, biliary ducts were not dilated, liver parenchyma had a homogeneous aspect, and portal and hepatic circulation were normal. Hepatitis viral serology was negative. Ceruloplasmine, serum copper concentration and alpha 1-antitrypsin were normal. Transaminase levels returned to normal

limits within one week, followed by a slower decrease of alkaline-phosphatase and gamma-glutamytransferase levels, which returned to the patients' baseline values.

Initial treatment with oxacillin was changed to vancomycin, followed by teicoplanin, which in turn were replaced by linezolid after 10 weeks because of glycopeptide-related renal toxicity (vancomycin) and thrombocytopenia (teicoplanin). Meropenem was added for coverage of Gram-negative pathogens. With this antibiotic regimen, the patient improved clinically and inflammatory parameters decreased gradually, but symptoms of anorexia and weight loss persisted, necessitating placement on parenteral nutrition. She was discharged from the hospital 4 months after the removal of the prosthesis. Six days later she was re-admitted to the emergency department with general weakness and itching, right hypochondrial and epigastic pain, nausea and vomiting since four days. Her family had noticed yellow discoloration of the sclerae since two days. At that time, she was taking linezolid (600 milligrams every 12 hours) and meropenem (one gram every eight hours) for respectively 50 days and was receiving home total parenteral nutrition (Structokabiven 12g N (Fresenius®), supplemented with vitamins and oligo-elements) for 36 consecutive days. Additional medication consisted of vitamin D, calcium, domperidon, esomeprazol, enoxaparine and dorzolamide- timolol eye drops.

Upon admission clinical examination showed an icteric and dehydrated patient in poor general condition. Her vital signs were a temperature of 37°C, a pulse rate of 103/min, a blood pressure of 11/6 cmHg and a respiratory rate of 36/min. The abdomen was tender, especially in the right hypochondric region, but there was no peritoneal irritation. On admission blood analysis showed a severe lactic acidosis: pH 7.27 (normal 7.35-7.45), bicarbonate 11.2 mmol/l (normal 22-26), lactate 121 mg/dl (normal 9-16) and cholestasis (gamma-glutamyltransferase 559 U/l (normal 9-36), alkaline phosphatase 2486 U/l (normal 30-120), total bilirubin 12.1 mg/dl (normal 0.3-1.2), direct bilirubin 8.83 mg/dl (normal 0-

0.30). Transaminases were slightly elevated: aspartate aminotransferase (AST) 97 U/l (normal 0-31), alanine aminotransferase (ALT) 113 U/l (normal 7-31) and thrombocytopenia was present: 84.000/µl (normal 177.000-393.000). The prothrombin time was 50% (normal 70-120). The prothrombin time, expressed as percentage, is The serum ammonia was elevated up to 86 µmol/l (normal 11-48). She also had a mild elevation of the serum creatinine on admission of 1.07 mg/dl (normal 0.55-0.96).

The patient was admitted to the intensive care unit because of progressive encephalopathy, grade 3 (presence of apathy and somnolence and disorientation). In the presence of impaired synthetic function (decreased prothrombin time and spontaneous hypoglycaemia) encephalopathy and icterus having occurred within less than six weeks , a diagnosis of acute liver failure was made. Initially, she was hemodynamically and respiratory stable. There were no signs of cardiac ischemia based on cardiac enzymes, electrocardiography and transthoracic echocardiography. There were no focal signs of intercurrent infection. Linezolid, meropenem and total parenteral nutrition were discontinued and continuous hemodialysis was started because of persistent lactic acidosis within 24h of ICU admission.

Further investigations were performed. Viral serology and antimitochondrial antibodies were negative. Antinuclear factor was positive, which was attributed to rheumatoid arthritis. Anti-smooth muscle antibodies were mildly elevated. There was no hepatomegaly nor dilatation of the biliary ducts on abdominal ultrasound and Magnetic Resonance Choledochopancreaticography (MRCP). The liver parenchyma had a heterogenous aspect on Magnetic Resonance Imaging (MRI). The duplex doppler examination of the liver and portal system was normal. A Computed Tomography (CT) scan of the abdomen showed a diffuse oedematous thickening of the small intestine wall and colon wall, and the presence of intra-abdominal free fluid. During a diagnostic explorative laparoscopy, for which she was

electively intubated, there were no arguments for ischemia of small and large intestine. The blood supply to all other abdominal organs was preserved. A liver with a rough surface but normal size was seen. A subcapsular liver biopsy was performed. Light microscopy revealed preserved architecture of the liver parenchyma, with the presence of diffuse and mainly microvesicular steatosis. The pas-diastase staining revealed several ceroid macrophages, which were mainly localized in the centrolobular area. Some interlobular bile ducts showed a flattened, damaged epithelium and the staining for cytokeratin 7 revealed that some portal tracts contained no bile duct. In agreement with these findings, the cytokeratin 7 staining also showed periportal ductular reaction and cholate stasis. Overall, this subcapsular liver biopsy showed diffuse microvesicular steatosis and features compatible with toxic parenchymal liver damage with associated bile duct damage (Figures).

The patient could not be weaned from the ventilator postoperatively due to the encephalopathy. Lactic acidosis resolved over a few days. Hemodialysis was discontinued after four days and enteral nutrition was started. The prothrombin time increased but cholestasis persisted. Repetitive ultrasound revealed no dilated intra- or extrahepatic bile ducts. The patient was weaned from the ventilator after 12 days of mechanical ventilation, and could be discharged from the intensive care unit (ICU) after 16 days. Bilirubin levels normalized within 14 weeks. In this period alkaline phosphatase and gamma-glutamyltransferase levels returned to the patients' baseline values (Graphs).
Meropenem was restarted one month later because of persisting osteomyelitis, and no increases in liver function tests were observed. The patient however died 4 months after her first ICU admission because of uncontrollable septic shock.

Discussion

Our patient presented with lactic acidosis and fulminant liver failure, as shown by the development of icterus and encephalopathy within less than 6 weeks; hypoglycaemia and a rise in INR were further signs of liver failure. Linezolid was thought to be the probable cause of this event. Drug-induced liver injury (DILI) has been associated with the use of nearly 1000 drugs, and may mimic all forms of acute and chronic hepatobiliary disease.[5,6] Establishing a definite diagnosis of DILI is challenging and often impossible. *Cornerstones in establishing a likely diagnosis of DILI are the exclusion of other etiologies of liver injury, a time course congruent with the introduction of the drug and recovery after withdrawal of the drug, and a clinical and/or histological signature compatible with postulated mechanisms of drug-induced toxicity*. The Council for International Organizations of Medical Sciences/Roussel Ucalf Causality Assessment Method scale [6,7,8], is developed to quantify the strength of the association between hepatic injury and medication as its suspected cause, *(implicated as causing the injury.)* The system comprises seven weighted criteria (time to onset following initial drug exposure, course of the reaction, presence of risk factors, concomitant drug exposure, exclusion of non-drug causes of liver injury, previous information regarding the known hepatotoxic potential of the drug and response to re-challenge), that are tabulated and taken into consideration in a graded fashion along with the type of liver injury (hepatocellular or cholestatic/mixed). We found a score of 6 in our patient, which corresponds to a probable association between linezolid and DILI. DILI was complicated by acute liver failure, since icterus and encephalopathy developed within a time frame of 6 weeks; additional signs of liver failure were hypoglycemia and a decrease in prothrombin time. (*the occurrence of microvesicular steatosis with acute liver failure was probable (score 6).)* Elevation of liver enzymes in patients treated with linezolid have been described before, but severe DILI or liver failure has not yet been reported. (Linezolid use may occasionally be associated with abnormalities in liver enzymes.[4] (*The degree of derangement varies, likely based on the*

patient population and associated comorbidities.) Liver failure related to the use of linezolid however has not been reported before)

(*In our patient*,) We intensively sought for alternative causes of liver injury. Screening tests for viral hepatitis, hereditary hemochromatosis, α1- antitrypsin deficiency and Wilson's disease were negative, and medical imaging ruled out biliary obstruction, cardiac dysfunction or hepatic vascular abnormality. The liver did not show ischemia on laparoscopy. (There was no dilatation of the biliary ducts on abdominal ultrasound and MRCP, and vascular abnormalities were ruled out by duplex doppler examination of the liver and portal system. Peroperative there were no arguments for ischemia. Echocardiography showed a normal left ventricular function. Our patient had a positive antinuclear factor test and a mildly positive anti-smooth muscle antibodies. However) Despite the presence of some anti-smooth muscle antibodies, light microscopy of the liver biopsy showed no (*evidence for*) auto immune hepatitis or primary biliary cirrhosis. (*An immune-mediated idiosyncratic reaction characterised by the presence of fever, rash, eosinophilia and auto-antibodies (such as antinuclear and smooth muscle antibodies) is described with DILI*.[6])

We reckoned toxicity induced by therapy given alongside linezolid, more precisely meropenem and total parenteral nutrition. (*The patient was taking linezolid and meropenem for respectively 50 days and was receiving home total parenteral nutrition for 36 consecutive days*.) Parenteral nutrition is a known cause of liver dysfunction, ranging from mild elevations of serum aminotransferases, alkaline phosphatase and bilirubin, to steatosis, steatohepatitis (predominantly in adults), and cholestastis (predominantly in infants). When steatosis is related to the use of parenteral nutrition, macrovesicular steatosis is the predominant finding observed on biopsy specimen.[9] Scarce articles describe both microvesicular and macrovesicular steatosis with the use of parenteral nutrition.[10] The purely microvesicular steatosis with associated bile duct damage in our patient, coupled with

the fulminant course of liver dysfunction, argues against parenteral nutrition as main etiology. The possibility remains however that total parenteral nutrition has contributed to the development of severe DILI. (predisposed our patient to develop severe liver injury by linezolid.)

Elevation of liver function tests during meropenem therapy has been described in 2 to 5 percent of the treated patients.[11] A more thorough search of the literature showed no reports on severe hepatic failure or microvesicular steatosis. In our patient meropenem was rechallenged in September during a new septic episode due to osteomyelitis without recurrence of elevation of the transaminases. (liver function tests.)

Linezolid use may occasionally be associated with abnormalities in liver enzymes.[4] The degree of derangement varies, likely based on the patient population and associated comorbidities. Liver failure related to the use of linezolid however has not been reported before. As linezolid toxicity was considered to be the cause of the lactic acidosis and the concomitant hepatic failure, the antibiotic was withdrawn. As the metabolic acidosis could not be controlled with a continuous sodiumbicarbonate infusion, hemodialysis was started. Thiamine has been used in the treatment of linezolid-induced lactic acidosis, but is no proven therapy.[12] Our patient already received thiamine at home which was continued. Lactate levels normalized within four days, INR, fibrinogen and thrombocytes recovered within two weeks, but cholestasis persisted. This time course is congruent with that of previous case reports of patients surviving linezolid-induced lactic acidosis, which showed resolution of hyperlactatemia within 2 days to 2 weeks following linezolid withdrawal.[12] Noteworthy, resolution of DILI after to drug withdrawal may be delayed, in particular the cholestatic pattern which may take up to 1 year to resolve.[13]

In our patient, the predominant pattern of liver histology was that of diffuse microvesicular steatosis. Microvesicular steatosis is related to severe impairment of the mitochondrial ß-oxidation of fatty acids. It is identified by the presence of small, uniform lipid droplets dispersed throughout the hepatocyte, which leave the nucleus in the centre of the cell. Microvesicular steatosis is a potentially severe form of hepatotoxicity, which, in severe cases, may rapidly evolve to liver failure, coma and death. While some hepatocytes exhibit microvesicular fat, other may exhibit macrovacuolar steatosis in the same patient. These mixed cases should be classified as microvesicular steatosis, since the latter may entail a more severe prognosis.[14,15,16] Various endogenous and exogenous substances impair mitochondrial ß-oxidation to cause microvesicular steatosis (Table 2). Our patient was not taking any of these medications (*associated with the development of microvesicular steatosis*), and she denied the use of any over-the-counter drugs, herbal products or alcohol.

Linezolid exerts its antimicrobial effect through inhibition of bacterial protein synthesis by binding to the 23S ribosomal RNA of the 50S subunit. The mitochondrial protein synthesis machinery is in many ways similar to the prokaryotic machinery and as a result may be a collateral target for antibiotics that function by binding to the bacterial ribosome.[17] This is well illustrated by the fact that tetracyclines, which have a similar microbial target as linezolid, are associated with the occurrence of microvesicular steatosis as well.[14] Mitochondrial dysfunction is also the key mechanism responsible for linezolid-induced lactic acidosis. Previous studies have shown that linezolid induces a dose- and time- dependent inhibition of mitochondrial protein synthesis.[2,18] Interestingly, in the lactic acidosis case patient of De Vrieze et al., macro- and microvesicular steatosis was also seen on histological examination of liver samples. In contrast to our patient, elevation of the liver function tests or clinical symptoms associated with liver failure, with the exception of encephalopathy, were not mentioned for this case patient who was admitted with optic neuropathy, myopathy, lactic

acidosis and renal failure after prolonged use of linezolid. Finally, it should be mentioned that other antimicrobial oxazolidinones, more precisely the early derivatives investigated by DuPont in the 1980s,[19] and newer potent molecules (PNU-140693 and PNU-141059) [20] are known to induce hepatic toxicity in animal models. The association of lactic acidosis with microvesicular steatosis and occasionally liver failure has been well known in patients receiving nucleoside-analogue reverse transcriptase inhibitors (NRTIs).[21] However, it should be noted that NRTIs inhibit the mitochondrial DNA polymerase-γ while linezolid inhibits the mitochondrial protein biosynthesis.

The fact that our patient presented with preexisting signs of cholestasis (elevated alkaline phosphatase and gamma-glutamyltransferase levels upon admission in April) is a limitation in this report. (When the hip prosthesis was removed and oxacillin was started, a transient elevation in transaminases, alkaline phosphatase and gamma-glutamyltransferase was observed, on the other hand bilirubin and thrombocyte count remained normal. Transaminase levels returned to normal limits within one week.) As our patient already had received multiple antibiotic regimens and parenteral nutrition, the presence of an underlying pre-existing liver injury is possible. However, from the time course of liver function tests, it (As transaminases, bilirubin and lactate were normal with the start of linezolid, and as alkaline phosphatase and gamma-glutamyltransferase levels already returned to the patients' baseline values (graphs),) shows that treatment with linezolid coincided with the occurrence of a new hepatotoxic event (we can assume that the start of linezolid in combination with meronem and parenteral nutrition gave rise to a new hepatotoxic event.)

In conclusion, we report on a patient developing lactic acidosis and DILI with acute (*fulminant*) liver failure, probably related to prolonged use of linezolid. Clinicians should be aware of this rare but life-threatening adverse effect.

(Summary

We describe a case of severe liver injury and lactic acidosis after prolonged use of linezolid. Lactic acidosis has been reported almost exclusively in patients treated for longer than the maximum recommended duration of 28 days. This report suggests the risk for major toxicity associated with prolonged courses of linezolid. Prescribers should be aware of the possibility of linezolid induced liver injury when a patient presents with severe cholestasis or liver failure.) weglaten

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Legends:

Figure 1 : the parenchyma shows diffuse microvesicular steatosis (arrows). (Original magnification x400).

Figure 2: portal tract with a mildly increased mononuclear infiltrate and a bile duct with damaged, degenerated epithelium containing a lymphocyte (arrow). (Original magnification x400).

Figure 3: the CK7-staining shows a portal tract with a damaged bile duct (long arrow), periportal ductular reaction (short arrows) and positive periportal hepatocytes,

indicating cholate stasis (arrowhead). Note that the stained hepatocytes appear vacuolated due to the microvesicular steatosis. (Original magnification x400).