A man in his seventies with a long-term infection and severe acid-base imbalance

A man in his 70s with complicated diabetes, cardiac disease and long-term antibiotic treatment owing to a toe infection was admitted to hospital with a severe acid-base imbalance. He developed a life-threatening condition that required intensive care treatment. An assessment to determine the cause of the acid-base imbalance was initiated concurrently with life-saving treatment.

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A man in his 70s was admitted to hospital in reduced general condition, with dyspnoea, oliguria, nausea, anorexia and blood extravasation. He had existing hypertension, atrial fibrillation, a mechanical aortic valve and type 2 diabetes mellitus with nephropathy, neuropathy and retinopathy. He had started exercising and had adopted a healthier lifestyle.

The patient had been discharged nine days before the events in question after a month in hospital due to sepsis stemming from a toe infection. During his stay in hospital the toe was amputated, and the antibiotic regime was changed several times. Because of third-degree atrioventricular block a pacemaker was inserted.

At the time of readmission he was using warfarin for atrial fibrillation and a mechanical valve, metoprolol, lercanidipine, irbesartan, hydrochlorothiazide, furosemide and moxonidine for hypertension, allopurinol for uric acid gout, linezolid for infection and pravastatin as a cholesterol-lowering medication.

At the first clinical examination, the patient was mentally lucid. He felt lethargic, but was without pain. He had normal blood pressure and an irregular heart rate of 85 BPM. Oxygen saturation was 97 % on room air, but the patient was dyspnoeic. He had an extravasation on the left upper arm. FOB was negative. Tests on admission showed C-reactive protein (CRP) 3 mg/l (< 5 mg/l), haemoglobin 7.3 g/100 ml (13.4–17.0 g/100 ml), platelets (TPC) 142 · 10^9/l (145–348 · 10^9/l), prothrombin time (INR) 3.2 (therapeutic range 2.5–3.5), haptoglobin < 0.1 g/l (0.5–2.1 g/l), glucose 11.0 mmol/l (4.0–6.0 mmol/l), creatinine 245 μmol/l (60–105 μmol/l), sodium 133 mmol/l (137–145 mmol/l) and potassium 4.8 mmol/l (3.5–5.0 mmol/l). The patient was admitted to the Department of Medicine with a diagnosis of anaemia and dehydration and received 1 l saline and two bags of SAGMAN solution.

There were no cardiac findings or signs of a flaring up of the infection, but the patient had low haemoglobin. Haptoglobin binds free haemoglobin in plasma, and the low value could indicate haemolysis. A mechanical aortic valve can cause haemolysis, but this seldom results in such severe anaemia (1). The patient used warfarin and was susceptible to bleeding, with INR in the upper therapeutic range, but apart from one exravasation on his arm, no source of bleeding was found. Negative FOB excluded gastrointestinal bleeding.

He had dyspnoea, but his oxygen uptake was normal. Severe anaemia may cause a rapid respiratory rate, but with symptomatic anaemia leading to dyspnoea, tachycardia would also be expected (2). However, the patient was on the betablocker metropolol, which lowers the heart rate. The emergency doctor concluded that anaemia was the cause of his symptoms, and gave the patient a blood transfusion.

The patient had known nephropathy, and on admission he had a substantially affected kidney function with elevated creatinine and low sodium. The emergency doctor concluded that dehydration was the cause of his oliguria. The patient was using the angiotensin II receptor blocker irbesartan. In cases of dehydration and impaired kidney function, angiotensin II blockers may cause renal failure (3). Chronic renal failure may also result in anaemia owing to inadequate production of erythropoeitin.

Arterial blood gas is a simple test that may yield useful information in the event of both dyspnoea with no known cause and acute renal failure. The test was not carried out in the Emergency Department, but venous base excess (BE) was ordered for the following day.

Blood tests the day after admission showed venous BE –18 mmol/l (–3.0–3.0 mmol/l), haemoglobin 10 g/100 ml, TPC 125 · 10^9/l , INR 4.1, glucose 11 mmol/l, sodium 137 mmol/l, potassium 5.2 mmol/l and creatinine 266 μg/l.

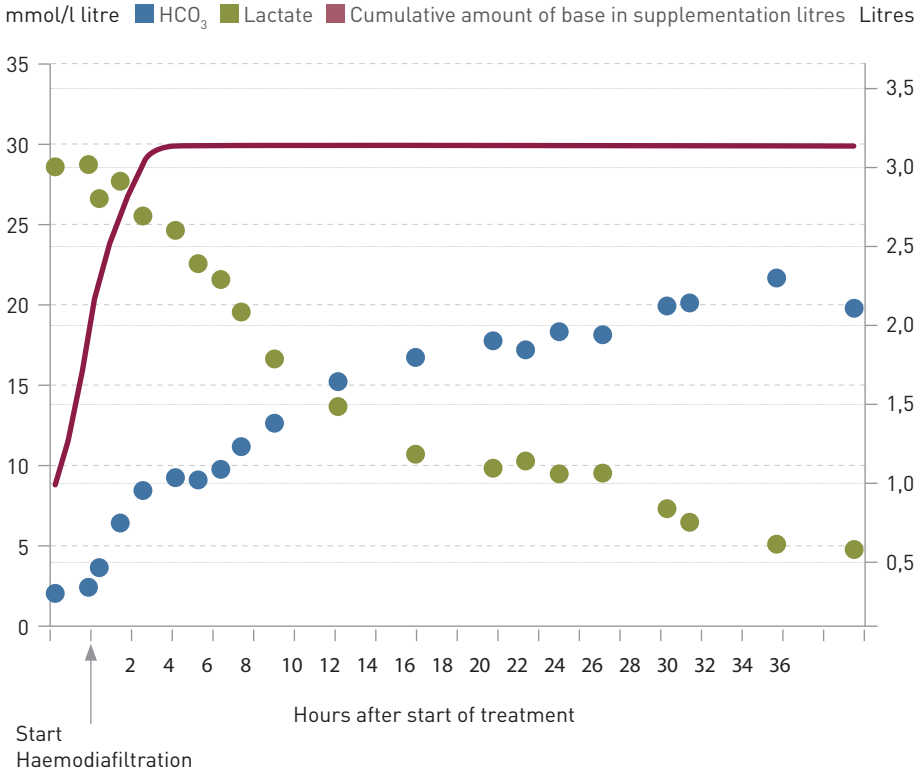

Figure 1 *Treatment with haemodiafiltration and base supplementation ($NaHCO_3$ 500 mmol/l and Tribonate) and the effect of the treatment on bicarbonate and lactate (mmol/l). The left y-axis indicates HCO_3 and lactate, the right base supplementation*

The patient felt increasingly breathless, and arterial blood gas showed pH 7.14 (7.36–7.44), BE –24 mmol/l (–2.5–2.5 mmol/l), pCO_2 (a) 1.4 kPa (4.5–6.1 kPa), HCO_3^- 3.0 mmol/l (22–26 mmol/l) and lactate 18 mmol/l (0.5–2.2 mmol/l). After 250 ml sodium bicarbonate 500 mmol/l, lactate was 22 mmol/l and pH 7.06, and a further 250 ml sodium bicarbonate and 400 ml Tribonate were administered. The intensive care doctor was contacted.

«Venous BE» is the arterial blood gas test «base excess» in venous blood. It is calculated on the basis of the bicarbonate (HCO_3^-) content and pH of blood and describes an excess of base in the patient. If a patient with a normal blood CO_2 level has a pH higher than 7.4, the patient has a base excess (positive BE), and accordingly metabolic alkalosis. With a pH lower than 7.4, the patient has a base deficit (negative BE) and metabolic acidosis (4).

Metabolic acidoses occur when there is a base deficit or excess acid. To distinguish between them, the anion gap is calculated. This is the difference between the numbers of important cations and anions $(Na + K) – (Cl + HCO_3^-)$. If there is an acid excess, the anion gap is increased, and if there is a base deficit, the anion gap is normal. Addition of the chloride anion (i.e. saline infusion) may result in a relative negative BE and acidosis with a normal anion gap (hyperchloraemic acidosis). Our patient had a low pH and negative BE, i.e. metabolic acidosis. The anion gap was 44 mmol/1 (10–16 mmol/l), i.e. there was excess acid.

Excess acid is found in patients who fail to eliminate acid, for example in cases of kidney or liver failure, or due to the production or addition of acids such as lactic acid, ketoacids or various toxins. The patient's anion gap of 44 mmol/l consisted of 16 mmol/l (upper normal range), 18 mmol/l lactate and 10 mmol/l «other». The patient had severe lactic acidosis. High kidney values and decreasing urine production indicated that kidney failure was contributing to the acidosis.

Lactate, the anion of lactic acid, is produced when there is an inadequate supply of oxygen for energy production via adenosine triphosphate (ATP) or when production is being blocked for other reasons (5). This happens in connection with exertion, hypoxia, inadequate blood supply or blockages in the energy production chain. A high lactate level is common with bowel necrosis and sepsis. Lactate is mainly metabolised in the liver, and liver failure can also result in lactic acidosis. Various drugs and toxins can interfere with the energy production in cells and raise the lactate level (cyanide, metformin, linezolid, propofol, zidovudine and adrenaline) (6). Metabolites of ethylene glycol may result in falsely elevated lactate in many blood gas analysers (7). Our patient had taken his drugs as usual the same day. He was not exposed to alcohol ingestion or smoke containing cyanide. He had no pain anywhere, and his stomach was soft, so abdominal ischaemia seemed unlikely. His CRP was 5 mg/l, and he was afebrile, so there was little risk of sepsis. His toe infection was unchanged, and he was still using linezolid which he had been taking for 23 days.

The patient had increasingly laboured breathing, but his oxygen saturation was fine, and blood gas tests showed pO_2 (a) 14.1 kPa (9.0–11.0 kPa). pCO_2 (a) 1.4 kPa is a very low value and a result of extreme hyperventilation. The respiratory centre reacts to high H^+ concentration with hyperventilation in order to raise a low pH. The pH value influences most chemical reactions in the body, and a stable, normal value has high priority in the body's metabolism. Hyperventilation is tiring, and when the patient gets exhausted his pH level will fall to dangerous levels (< 7.2), potassium may rise and cause cardiac arrest, the body's coagulation system will become ineffective, and the whole metabolism will be affected. pH < 7.0 is regarded as an extremely dangerous situation irrespective of the cause, and treatment must be initiated instantly. The most important goal is to eliminate the cause of the acidosis, but base supplementation and dialysis may help to stabilise the situation until definitive treatment can take place.

Despite base supplementation, the blood gas values deteriorated steadily with pH 7.03, BE –27 mmol/l, pCO2 (a) 1.4 kPa, HCO_3^- 3 mmol/l and lactate 27 mmol/l.

The patient was tachypnoeic and hypotensive and was transferred to the Intensive Care Unit(ICU).

On arrival at the ICU, lactate was 29 mmol/l, pH 7.01, glucose 2.9 mmol/l, TPC 113 · 10^9/l, alanine aminotransferase (ALT) 1 080 U/l (10–70 U/l) and INR > 7.5. Alkaline phosphatase (ALP) was normal and albumin just below the normal value. The patient was given concentrated glucose and plasma to correct his INR.

The body regulates pH by means of buffering, ventilation and renal correction. HCO_3^- is the body's most important base and buffer, and despite supplementation it was soon depleted. The patient was not capable of more hyperventilation, and began to tire. He was also undergoing acute chronic renal fail-

ure, so renal regulation of the acidosis was not effective. There was an impending risk of a fatal drop in pH. His lactate value continued to rise, and the situation was critical. Immediate massive intravenous buffering with base and dialysis were necessary.

Dialysis and haemofiltration are two different means of cleansing the blood in the event of renal failure. The treatment can be administered intermittently or continuously, and filtration and dialysis can be combined (haemodiafiltration). The treatment was administered to our patient in order to remove potassium, lactate, acid metabolites and any toxins, and to add bicarbonate.

Elevated ALT may indicate liver cell damage. Low albumin, low glucose and INR far above the therapeutic range show synthesis failure. High gamma glutamyl transferase (GT) and ALP indicate intra- or extrahepatic cholestasis, and elevated lactate and ammonia indicate inadequate liver metabolic capacity. The patient's blood tests revealed acute hepatocellular damage without cholestasis, but with signs of functional impairment. The patient displayed no icterus.

Acute liver failure is seen in cases of intoxication, cholestasis, perfusion damage or hypoxia, as after circulatory arrest, in sepsis or blood clots in the liver circulatory system (portal venous thrombosis or Budd-Chiari syndrome) (8). There was no suspicion of cholestasis in the case of our patient. Thrombosis was unlikely in a patient undergoing anticoagulation therapy, but had to be excluded by means of liver ultrasound. Sepsis had to be suspected. The patient denied a high intake of ethylene glycol, methanol or paracetamol.

Acute liver failure is treated by eliminating the cause or administering an antidote if possible (acetylcysteine for paracetamol intoxication, dialysis for dialysable liver toxins, discontinuation or dose adjustment of all liver toxic drugs). Hypoglycaemia is corrected with glucose, severe hypoalbuminaemia with albumin, tendency to bleed with plasma, coagulation factors and vitamin K, and hypotension with vasopressin or other vasopressors. Liver dialysis (molecular adsorbents recirculating system – MARS) is available at Rikshospitalet in Norway's capital Oslo and is used as a bridge to liver transplantation or spontaneous recovery. Continuous renal replacement therapy can be used to remove lactate and correct the acidosis resulting from liver failure.

Blood cultures were taken, and an ultrasound of the liver revealed no pathology. After a review of the patient's list of drugs, all regular drugs were temporarily terminated because of acute liver and kidney failure.

Linezolid can cause lactic acidosis, thrombocytopaenia and anaemia, particularly in patients with kidney failure (9). The Norwegian Poison Information Centre recommended haemodialysis. In theory, with a low protein binding of 31 % and a distribution volume of only 40–50 l, linezolid lends itself to dialysis (10). Three hours of haemodialysis will remove 30 % of the linezolid and some of its two main metabolites (11).

We chose to combine haemodialysis treatment with haemofiltration in order to increase the effect on the acidosis, and administered a total of 1 500 mmol of base (Fig. 1). Intubation was not an option, as the patient was conscious and did not have oxygenation failure. His respiratory compensation was so effective that his pCO_2 (a) fell to 1.3 kPa. Pressor therapy was necessary owing to hypotension.

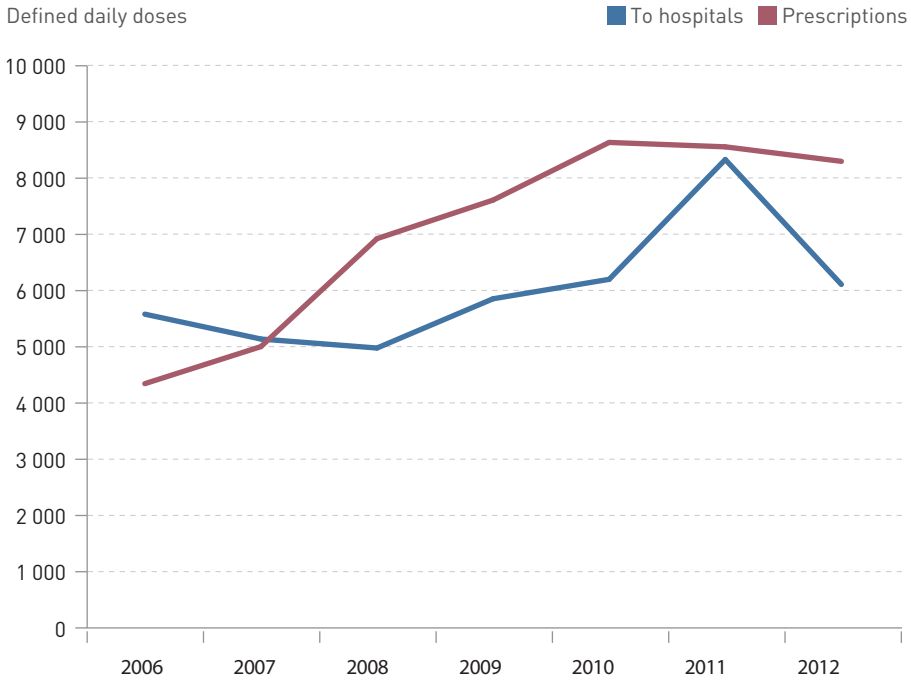

Figure 2 *Sales of linezolid in Norway 2006–12 as defined daily doses to hospitals (12) (with reservations for somewhat low figures for 2012 due to inadequate reporting) and outside hospitals) (13)*

The patient hyperventilated in order to compensate for acidosis, which was still at a critical level. In such situations, intubation may lead to less hyperventilation, a fall in pH followed by a rise in potassium and a possible cardiac arrest. The patient should therefore breathe independently for as long as possible, with emergency intubation as plan B.

About 1.5 hours after the commencement of haemodiafiltration and aggressive base supplementation, his readings were pH 7.2, BE –20, pCO_2 (a) 2.3 kPa, HCO_3^- 7 mmol/l and lactate 27 mmol/l. The patient already felt better. His blood gases were monitored closely during the night (Fig. 1).

The following morning pH was 7.44, BE -8, pCO_2 (a) 3.1 kPa, HCO_3^- 16 mmol/l and lactate 14 mmol/l. ALT had risen to 4 100 U/l and TPC had fallen to 85 · 10^9/l. The patient felt better but was still tachypnoeic and oliguric. Vasopressor was discontinued the same day.

Three days after admission lactate was 3.0 mmol/l, and his liver values began to fall, while TPC fell to 23 · 10^9/l. His blood culture was negative.

Haemodiafiltration was continued for two days. The patient was moved to the Renal Department after three days in the ICU. Lactate was then in the normal range and TPC rising. The patient received intermittent dialysis for a further three days. He managed without dialysis subsequently, but his kidney function remained considerably impaired. Three weeks later his liver tests were normal. His toe infection never healed, and a leg amputation was performed.

Discussion

The patient's symptom picture with lactic acidosis, liver and kidney failure, anaemia and thrombocytopaenia, could fit several diagnoses, most likely sepsis. The patient's good mental condition and lung function, coupled with low infection variables, weighed against sepsis.

Instead, suspicion was directed at linezolid (Zyvoxid®), which is an oxazolidinone antibiotic with the property of inhibiting protein synthesis in gram positive bacteria (10). Linezolid is used widely for infections with

methicillin-resistant staphylococcus aureus (MRSA) and as secondary treatment for multi-drug-resistant tuberculosis (MDR-TB).

In Norway linezolid is approved for treating pneumonia and soft tissue infections, but is used mainly for prosthetic joint infections, osteomyelitis and endocarditis, particularly with infections caused by coagulase-negative staphylococci and ampicillin-resistant enterococci (11). The drug is also used as an oral alternative to vancomycin. Consumption of the drug is increasing in Norway (Fig. 2) (12, 13).

The symptoms tallied well with suspicion of an adverse reaction to linezolid, and haemodiafiltration was already proving effective after one and a half hours of treatment.

Blood samples were sent to the Antimicrobial Reference Laboratory in Bristol to determine the serum concentration of linezolid (14). The serum concentration was 35.7 mg/l at 8 a.m. and 6.35 p.m. and 31.1 mg/l at 7.35 p.m. The patient used linezolid tablets 600 mg 12-hourly (at 8 a.m. and 8 p.m.). The evening dose was discontinued, and haemodiafiltration commenced at 6.50 p.m. Three hours of dialysis removes 30 % of linezolid (15), i.e. about 3 mg/l in the course of 45 minutes. This tallies well with our measurements.

The first and second samples represent virtually minimum values (C_{min}), since both were taken a short time before the next dose. C_{min} and C_{max} normal values are 3.80 mg/l (1.75–7.53 mg/l) and 14.70 mg/l (10.57–19.64 mg/l) (median value (interquartile range)) in equilibrium (16). Our patient had a very high serum concentration.

Linezolid metabolises largely to inactive metabolites that are eliminated renally. The concentration of the metabolites increases in severe renal failure (15). Whether the linezolid concentration increases in renal failure is open to discussion, even though 30 % of the drug is excreted unchanged in the urine (17). Brier et al. found no increase in dialysis patients after a single dose of linezolid (15), but Sasaki et al. maintain that renal failure substantially reduces linezolid clearance, particularly in the case of treatment for more than two weeks, and that the dose should be halved in the event of creatinine clearance < 30 ml/min. They suggest that the mechanism is autoinhibition of linezolid metabolism after repeated doses, and that saturation of non-renal metabolism increases the contribution of renal failure with time (9). A switch to non-linear pharmacokinetics in the presence of impaired liver and kidney function could result in accumulation of linezolid and metabolites, and case reports have revealed a high linezolid level in dialysis patients (18).

The Norwegian Pharmaceutical Product Compendium (Felleskatalogen) recommends linezolid 600 mg 12-hourly by mouth or intravenously for up to 14 days without dose adjustment in cases of liver or kidney failure. Treatment in excess of 28 days is not recommended (10). In patient material from Oslo University Hospital, Ullevål, seven of ten patients with MDR-TB had to discontinue linezolid 1 200 mg/day for 6–40 weeks because of adverse events (19). The frequency of serious adverse events in connection with long-term treatment appears to be dose-dependent. In a study where treatment with daily doses of 600 mg or 300 mg linezolid proceeded for 18 months, only three of 38 patents had to discontinue linezolid treatment before the scheduled time. The lowest dose resulted in the lowest adverse event frequency, but the same infection control (20).

Our patient had a creatinine level of 143 µg/l when linezolid treatment started, and known diabetic nephropathy. The serum concentration of linezolid was extremely high after development of lactic acidosis. At that time the patient had also developed severe liver failure. Linezolid clearance falls by 50 % in the event of severe cirrhosis of the liver (9). We have not found documentation to the effect that acute liver failure affects linezolid metabolism. Whether the cause of the high linezolid serum level was due to liver and/or kidney failure, treatment with the drug for 23 days, or a combination of factors is unclear.

Lactic acidosis in connection with linezolid treatment was first described by Apodaca and Rakita in 2003 (6) and has since been reported a number of times. Linezolid functions through selective inhibition of bacterial protein synthesis and accordingly by inhibiting bacterial growth and reproduction. Garrabou et al. have demonstrated that the cause of lactic acidosis in connection with linezolid treatment is a blockade of the last enzyme in the electron transport chain that leads to production of ATP in the mitochondria (21).

Thrombocytopaenia is a known adverse effect of linezolid treatment (9). In our patient the platelet concentration was normalised nine days after termination of linezolid.

Acute liver failure as a side effect of linezolid treatment after long-term use has only previously been described in a single patient report (22). Our patient's liver function was normal three weeks after termination. An ultrasound scan of the liver was normal, but the patient regularly used a total of seven drugs that have various adverse effects on the liver. The interaction database of Norwegian clinicians showed no drug interactions between the patient's regular drugs (23).

Anaemia is a well known side effect of linezolid (24). Two weeks after termination of linezolid, his haemoglobin was > 12 g/100 ml.

Linezolid has side effects that are potentially very dangerous, especially in connection with long-term use, and in cases of liver and kidney failure. Complex pharmacokinetics, particularly in critically ill patients, point to the need to establish a national service for determining the concentration of serum linezolid. A lower daily dose than 1 200 mg must be considered for patients with liver or kidney failure. The risk of adverse effects points to a need for close monitoring. We propose that liver and kidney tests be checked before starting the medication, and haemoglobin, TPC, creatinine, carbamide and linezolid concentration two weeks after treatment commences and then every two weeks.

The reasons usually given for exercising caution in the use of antibiotics are allergies, interactions and development of resistance in individual patients and resistance to bacteria in the population at large. Our patient's history shows that some anti-bacterial agents may in rare cases have lethal side effects.

The patient has consented to the publication of the article.

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