CASE REPORT

Linezolid-induced pancytopenia

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SUMMARY

Linezolid is a bacteriostatic antibiotic of the Oxazolidinone class; it works by inhibiting the initiation of protein synthesis on bacterial ribosomes. Due to its excellent bioavailability after oral dosing, it has become an important tool in combating multi-drug-resistant bacteria including glycopeptide-resistant enterococci and methicillin-resistant *Staphylococcus aureus*. Side effects are multiple and potentially serious. We report the case of an 87-year-old man who developed pancytopenia secondary to a 6-week course of linezolid. Withdrawal of the antibiotic was decided as the treatment and resolution of the pancytopenia was evident within 2 weeks. Clinicians should be aware of this side effect of linezolid therapy and that weekly full blood count monitoring is paramount.

BACKGROUND

Although bacteriostatic, linezolid has huge clinical benefit in that it is effective against hard to eradicate Gram-positive bacteria such as glycopeptide-resistant enterococci and methicillin-resistant *Staphylococcus aureus*. Common side effects attributed to the medication include diarrhoea, headache, anaemia, taste disturbance and nausea but a number of less common side effects including blurred vision, leucopenia, neutropenia, thrombocytopenia and pancytopenia have been reported in the literature.

With pancytopenia developing for several reasons, not limited to hypothyroidism, myelodysplastic syndrome, viral infections, sepsis and bone marrow invasion, it is important to consider drug causes in the list of differentials. Not solely because lack of awareness can lead to unnecessary investigation and further progression of the pancytopenia with resultant complications of severe infection, bleeding and anaemia.

Here we describe the development of pancytopenia after 6 weeks of linezolid in a patient with a glycopeptide-resistant enterococci positive joint swab post total knee replacement and joint washout. This was an extended off-label prescription of linezolid on discussion with Medical Microbiology.

CASE PRESENTATION

An 87-year-old Caucasian man was admitted to the Acute Medical Unit at our hospital in February 2018 with an asymptomatic pancytopenia found on monitoring of his full blood count (FBC) by the general practitioner (GP).

The patient had undergone a total knee replacement early December 2017 with subsequent washout and debridement 2 weeks later due to wound breakdown. Following the washout, the patient was initially treated with benzylpenicillin and flucloxacillin which was later switched to linezolid and piperacillin based on microbiology culture results. Cultures had revealed a deep swab positive for glycopeptide-resistant *Enterococcus*, mixed anaerobes, *Streptococcus mitis* and *Pseudomonas stutzeri*, and the overlying wound swab was positive for *S. aureus* and non-lactose fermenting coliforms. It is important to clarify that this was a wound failure rather than a deep infection. On discharge the oral step down antimicrobial plan was discussed at the multidisciplinary team meeting. The decision was to prescribe a 6-week antimicrobial triple-therapy regime (linezolid 600 mg twice daily, metronidazole 400 mg three times daily, ciprofloxacin 750 mg twice daily) as a 'belt and braces' approach, with planned weekly FBC monitoring in primary care. Orthopaedic follow-up was initially planned for weeks 2 and 4.

The patient was referred to the Acute Medical Unit by his GP 5 weeks into triple-therapy treatment, history of presenting complaint confirmed the patient had been asymptomatic, that his total knee replacement was providing good function and that he was due an appointment at the Orthopaedic clinic in 1 week with a view to stopping the antibiotics. No weight loss, night sweats, bruising, breathlessness or fever were reported. The patient had a background of chronic kidney disease stage 3, transient ischaemic attack, atrial fibrillation, hypertension, osteoarthritis of the knees and high cholesterol. In addition to the antimicrobial triple therapy, he was also concurrently taking: atenolol, warfarin (target International Normalized Ratio (INR) 2.5), simvastatin, ramipril and a recent course of folic acid and ferrous fumarate prescribed by the GP on the basis of a falling haemoglobin.

The patient confirmed he lived alone in a bungalow with good family support, he reported normal activities of daily living with the aid of a walking frame and improving exercise tolerance, being able to walk a good 500 metres since his total knee replacement. He was an ex-smoker and drank eight units of alcohol per week as beer.

INVESTIGATIONS

On physical examination at admission he appeared to be alert and orientated and was

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haemodynamically stable. His oxygen saturation was 99% on room air, respiratory rate 17 coupled with vesicular breath sounds throughout all lung fields. His blood pressure was 151/87 mmHg with an irregularly irregular pulse of 90 beats per minute, heart sounds were normal as was jugular venous pressure. Glasgow Coma Scale was 15/15, temperature 35.5 (this was a one-off anomalous reading that normalised to 36.9 when rechecked 30 min later and remained within normal range) and capillary blood glucose 6.1. His abdomen was soft non-tender with normal bowel sounds and no organomegaly. No rashes, lymphadenopathy or spontaneous bleeding/bruising were noted and the right knee appeared to have healed well with 0–115° of pain-free movement, stable ligaments and no overlying effusion or erythema. The knee had healed without incident and was providing the patient with a good result.

In light of the GP blood results showing a pancytopenia and the range of differentials that could cause this, the following bloods were requested: group and save, haematinics, iron studies, full blood count, bone profile, liver function test, urea and electrolytes, clotting screen, INR, C-reactive protein, thyroid function tests, blood film and myeloma screen.

RESULTS

- ▶ Group and save: group A Rh+ve.
- ▶ Haematinics: B12 431 (normal), folate 8.4 (normal), ferritin 807 (high).
- ▶ Iron studies: iron 32 (high), iron binding capacity 32 (low).
- ▶ Full blood count: haemoglobin 78 (low), white cell count 2.7 (low), platelets 79 (low), haematocrit 0.22 (low), red cell distribution width 14 (normal), mean corpuscular volume 84.2 (normal) (please see [table 1](#) for a detailed timeline of FBC results).
- ▶ Bone profile: albumin 33 (low), adjusted calcium 2.30 (normal), alkaline phosphatase 63 (normal).
- ▶ Liver function test: normal.
- ▶ Urea and electrolytes: sodium 131 (low), potassium 4.5 (normal), urea 6.2 (normal), creatinine 117 (normal).
- ▶ Clotting screen: activated partial thromboplastin time 40.7 s (high), prothrombin time 26.5 (high), INR 2.3.
- ▶ Thyroid-stimulating hormone: 2.86 (normal).
- ▶ C-reactive protein: 2 (normal).
- ▶ Blood film: 'Platelet count appears genuine, occasional large platelets'.
- ▶ Electrophoresis: 'No obvious monoclonal paraprotein detected'.
- ▶ Ig: IgM 0.22 (low).

DIFFERENTIAL DIAGNOSIS

- ▶ Linezolid-induced pancytopenia.
- ▶ Aplastic anaemia.
- ▶ Multiple myeloma.
- ▶ Myelofibrosis.
- ▶ Myelodysplasia.
- ▶ Pancytopenia secondary to hypothyroidism, B12 deficiency.

TREATMENT

Based on the inpatient blood results and mapping these to the recent FBC history, it was felt that the likely cause of the pancytopenia was the extended course of linezolid. A joint Haematology and Orthopaedic inpatient review was arranged, and it was agreed that linezolid was the likely cause. The verdict was to stop the linezolid and based on the asymptomatic nature of the presenting complaint and the haemoglobin being >70, the patient was discharged home with safety netting and a 2-week clinic review with follow-up FBC.

OUTCOME AND FOLLOW-UP

Unfortunately, the patient was unable to attend the follow-up appointment due to transport issues so the GP kindly agreed to carry out a FBC in community (9 March 2018). From these results it can be seen that both the platelet and white cell count had corrected and the haemoglobin was normalising, the Orthopaedic team had since stopped all antimicrobials and the GP had planned to review the FBC again in 1 month. A subsequent follow-up FBC (3 April 2018) demonstrated further improvement in haemoglobin levels, a slight dip in platelets that remained within the normal range and a further improvement in the white cell count.

DISCUSSION

Linezolid is a bacteriostatic antibiotic that works by inhibiting the initiation of bacterial protein synthesis on the bacterial ribosomes.¹ Due to its excellent bioavailability after oral dosing, it has become an indispensable tool to combat multi-resistant bacteria.^{1 2}

During pre-clinical trials of linezolid, myelosuppression was observed as a side effect, which appeared to be both time and dose-dependent and reversible on cessation of the drug.³ The British Medicines and Healthcare products Regulatory Agency summary of product characteristics report myelosuppression in patients receiving linezolid with the risk of these effects being related to the duration of treatment.⁴ It has also been observed that patients' haematological parameters return towards pre-treatment levels on

Table 1 Full blood count results timeline

Event	Date	Haemoglobin (g/L)	Platelets (10 ⁹ /L)	White cell count (10 ⁹ /L)
	<i>Hospital normal range→</i>	140–180	140–450	4–11
Day 1 post washout	30 December 2017	112	232	13.7
Day 2 of linezolid+piperacillin	8 January 2018	106	238	5.9
Day 12 of linezolid, day 3 of triple therapy	18 January 2018	110	123	5.9
Referred in by general practitioner—day 46 of linezolid, day 37 of triple therapy	21 February 2018	78	79	2.7
Linezolid stopped	22 February 2018	76	79	2.9
Day 16 after cessation	9 March 2018	89	224	4.7
Day 41 after cessation	3 April 2018	121	205	5.9

cessation of drug treatment.⁴ The decrease in values of our patient's FBC and subsequent rise after the treatment was discontinued reflect this finding.

Clinical trials of the drug reported thrombocytopenia in 2.4% of linezolid patients compared with 1.5% for controls and no cases of pancytopenia were reported.³ The 'Compassionate Use Program' however reported two cases of pancytopenia out of 828 treatment courses.⁵ After the use of linezolid was approved in the USA, there were 72 cases of haematological abnormalities reported among 55 000 patients within the first six months, of the 72 cases reported, pancytopenia accounted for 13 of these cases.² Lakhani *et al* reported a further case of pancytopenia with linezolid therapy.⁶ Though rare, the literature certainly recognises pancytopenia as a side effect.

The Naranjo algorithm⁷ used to determine the likelihood of an adverse drug reaction was used to establish the probability of the association between linezolid prescription and development of pancytopenia in our patient. The patient scored 6 on the Naranjo scale, indicating a probable association.

Approximately 30% of each linezolid dose is excreted unchanged via the kidneys, but it is reported that overall clearance is not markedly altered in cases of renal insufficiency.⁸ Indeed, the summary of product characteristics does not consider dose adjustments necessary for patients with renal impairment,⁴ but the British National Formulary advises metabolites may accumulate if the estimated glomerular filtration rate is <30 mL/min/1.73 m². While the summary of product characteristics states there is no need for dose adjustments in renal impairment, it should be noted that there have been several studies that have reported a significant relationship between thrombocytopenia and linezolid over-exposure in patients with renal impairment; therefore, there is an argument that renal impairment should be considered a risk factor.^{9–12} In this, it is possible that the patient's chronic kidney disease stage 3 contributed to the observed side effect.

It was felt unlikely that the patient's regular medications attributed to the pancytopenia as no interactions were noted and these drugs had been long-term prescriptions.

The recommendations from the summary of product characteristics state that close FBC monitoring should be offered to patients, particularly those who have a history of myelosuppression and those taking myelosuppressive medication.⁴

The biochemical mechanism of how linezolid causes pancytopenia is emerging. Current evidence supports the hypothesis that inhibition of mitochondrial protein synthesis, owing to an interaction of oxazolidinones with mitochondrial ribosomes, is the underlying cause.¹³ Bacterial ribosomes and mitochondrial ribosomes are both of prokaryotic origin and share similarities, which provides the theoretical basis of why linezolid binds to these mitochondrial ribosomes and thus causes loss of mitochondrial function in haemopoietic cells.^{13 14}

Learning points

- ▶ Linezolid is a cause of pancytopenia.
- ▶ Linezolid should be monitored with weekly full blood count (including platelets).
- ▶ Patients should be advised not to drive or operate machinery if they develop visual symptoms.
- ▶ Patients should report any visual disturbances, bruising, shortness of breath or signs of infection immediately.
- ▶ Courses of linezolid >28 days should be monitored with increased vigilance of side effects.

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