Reversal of linezolid-associated cytopenias, but not peripheral neuropathy, by administration of vitamin B6

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Objectives: We sought to determine if vitamin B6 therapy would reverse linezolid-associated cytopenias and/or peripheral neuropathy.

Patients and methods: We have recently treated two patients with disseminated Mycobacterium abscessus infections with prolonged (≥9 month) courses of linezolid. Both patients developed cytopenias related to linezolid, and one patient also developed peripheral neuropathy. Because continuing linezolid therapy was required, we administered vitamin B6 (50 mg orally once a day) in an attempt to mitigate the associated cytopenias.

Results: The cytopenias in both patients reversed following administration of vitamin B6, and stabilized during prolonged linezolid therapy, although the peripheral neuropathy did not.

Conclusions: Vitamin B6 treatment may be useful to prevent or modify the course of linezolid-associated cytopenias. More formal and rigorous study of vitamin B6 therapy in patients receiving prolonged courses of linezolid is warranted.

Keywords: pyridoxine, anaemia, thrombocytopenia, Mycobacteria, deficiency

Introduction

Linezolid is a first-in-class oxazolidinone antibiotic with broad-spectrum activity against Gram-positive cocci, anaerobes and atypical mycobacteria.1 Two major toxicities of linezolid are induction of cytopenias, particularly with prolonged courses of therapy,2 and peripheral neuropathy.3 We describe two patients infected with Mycobacterium abscessus who developed progressive cytopenias following prolonged administration of linezolid. One of the patients also developed peripheral neuropathy. Administration of vitamin B6 reversed the pancytopenias in both patients, but did not reverse the peripheral neuropathy.

Patients and results

Case 1

Patient A is a 64-year-old Filipina female with a history of pulmonary tuberculosis treated in the Philippines 4 years prior to her presentation with haemoptysis to Harbor-UCLA Medical Center. A computerized tomography (CT) scan of the chest revealed bilateral apical scarring, a right upper lobe subpleural nodule, right middle lobe bronchiectasis and a cavity in the right lower lobe. Multiple sputum specimens grew M. abscessus. While drug susceptibilities were still pending, treatment was initiated with amikacin [10 mg/kg intravenously (iv) once a day], clarithromycin (500 mg orally twice a day), cefoxitin (1 g iv three times a day) and linezolid (600 mg orally twice a day). Three weeks later, the patient’s antimicrobial regimen was narrowed to clarithromycin and linezolid based on the susceptibility results (susceptible to amikacin, clarithromycin and linezolid; intermediate to cefoxitin; resistant to ciprofloxacin, levofloxacin, doxycycline and trimethoprim/sulfamethoxazole). The patient was not taking any other medications during this time.

The patient presented to clinic for follow-up 2 months later and was found to have worsening anaemia, but not thrombocytopenia, by serial complete blood counts (CBCs; Figure 1a). The patient received a transfusion of four units of packed red blood cells and single dose of erythropoietin (40 000 units subcutaneous). Linezolid and clarithromycin were held. Subsequent laboratory studies demonstrated a low reticulocyte count and no evidence of haemolysis or gastrointestinal bleeding (Table 1).

After a week off linezolid, linezolid and clarithromycin therapy was resumed and administration of vitamin B6 (50 mg orally once a day) was initiated. The patient received two more weekly doses of erythropoietin. Follow-up CBCs over the next 5 months demonstrated persistently normal haemoglobin levels (Figure 1a). However, 4 months after re-initiating linezolid therapy, the patient began complaining of new onset, severe pain, numbness and burning in both lower extremities, radiating from her toes to her shins in stocking distributions. She had reduced sensation in these areas without weakness on physical examination. The pain grew progressively...
more intense and spread proximally to her knees over approximately a 2 week period. The linezolid and clarithromycin were held due to concern about linezolid-induced neuropathy. Vitamin B6 treatment was continued. Although proximal spread of the neuropathy ceased, the patient’s neuropathic symptoms persisted, with no improvement as of 6 weeks following termination of linezolid treatment.

**Case 2**

Patient B is a 41-year-old Hispanic male chronically taking prednisone for severe dermatomyositis and autoimmune hepatitis. He developed disseminated *M. abscessus* infection, with multiple positive cultures from sputum and from an arthrocentesis of a right knee effusion. He was treated with 6 weeks of amikacin iv (10 mg/kg once a day) and oral clarithromycin (500 mg twice a day) based on susceptibility testing (susceptible to amikacin, clarithromycin and linezolid; intermediate to cefoxitin; resistant to levofloxacin, imipenem, minocycline and trimethoprim/sulfamethoxazole). After 6 weeks, the amikacin was replaced with oral linezolid at 600 mg twice a day.

The patient’s subsequent course was complicated by multiple flares of his dermatomyositis and autoimmune hepatitis, requiring repeated pulse doses of corticosteroids. Five months after initiating linezolid therapy, the patient developed progressive pancytopenia (white blood cell count of 1300/mm³, haemoglobin 9.1 mg/dL, platelets 85,000/mm³; Figure 1b). Laboratory evaluation revealed no evidence of haemolysis or gastrointestinal bleeding, and his reticulocyte count (inappropriately normal in the face of marked anaemia) indicated his anaemia was from decreased red cell production (Table 1). A bone marrow biopsy confirmed that he had a hypocellular marrow, without evidence of infiltrative processes or granulomas. His steroid dose was not changed and the patient’s other medications, including sertraline, gabapentin, rofecoxib and famotidine, were continued. However, his linezolid and clarithromycin were held, and his pancytopenia spontaneously resolved with no other intervention, over the following week.

After a week off antibiotics the clarithromycin and linezolid were resumed and vitamin B6 (50 mg orally once a day) was added. The patient’s haemoglobin subsequently declined once again, and linezolid was held again 4 weeks later, while the B6 was continued. After another 2 weeks off antibiotics, the patient’s haemoglobin increased to the normal range and the patient complained of fevers, chills and cough. Linezolid treatment was, therefore, reinitiated, along with clarithromycin, due to concerns about recurrent mycobacterial infection. Subsequently *M. abscessus* was again cultured from an effusion in the patient’s right knee. Over the next 6 months, the patient’s haemoglobin remained stable at normal levels during combined linezolid/B6 therapy.

**Discussion**

Linezolid is a first-in-class oxazolidinone antibiotic with broad-spectrum antimicrobial activity. Although approved to treat infections caused by a variety of resistant Gram-positive cocci, linezolid also possesses good activity against anaerobes and atypical mycobacteria. Haematological toxicities caused by linezolid have been extensively described. For example, in a review of 2046 patients who received linezolid therapy in clinical trials, 9%, 4.1% and 4.7% of patients receiving more than 2 weeks of linezolid therapy developed worsening anaemia, thrombocytopenia and leucopenia, respectively. Although it is known that linezolid-induced cytopenias are due to reversible myelosuppression, there are no published data on the mechanism of this myelosuppression.

We describe two patients infected with *M. abscessus* who developed progressive cytopenias during prolonged (>9 months) administration of linezolid. Although both patients also received clarithromycin, we are unaware of any published reports linking cytopenias with clarithromycin. Patient A was taking no additional medications. Patient B was taking a variety of other medications; however, none of these medications was newly initiated at the time the pancytopenia developed, and the medications were continued even while the pancytopenia reversed. Hence, it is highly likely that the cytopenias in both patients were due to the continued administration of linezolid.
Although we strongly suspected linezolid as a cause for the cytopenias in our patients, the multidrug-resistant phenotypes of the *M. abscessus* strains infecting both patients limited other therapeutic options. Given the prolonged therapeutic course required, it was felt that amikacin was an unacceptably toxic second agent to administer with clarithromycin. In addition, an orally available drug was preferred. We therefore attempted to mitigate the cytopenias while continuing linezolid therapy. Vitamin B6 therapy was therefore initiated based on anecdotal communications.6

Vitamin B6 is required for synthesis of δ-aminolevulinic acid, a precursor of haem.7 Vitamin B6-responsive anaemias have been classically described as sideroblastic in the context of gene mutations affecting the haem synthetic pathway.7 True vitamin B6 deficiency may cause normocytic,8 microcytic9 or megaloblastic anaemias.8 For both of our patients, the timing of the reversal of their normocytic anaemias correlated with administration of vitamin B6, probably indicating that they had vitamin B6-responsive anaemias.

Although patient A also initially received a blood transfusion and several doses of erythropoietin, these treatments are highly unlikely to be responsible for maintenance of haemoglobin levels for an additional 7 months. Patient B presents a somewhat more complicated picture. Due to his polymyositis and autoimmune hepatitis, this patient probably had a component of anaemia of chronic disease. However, the temporal relationship between administration of linezolid and progressively worsening pancytopenia, the fact that an extensive evaluation (including a bone marrow biopsy) confirmed the presence of a hypoproliferative anaemia and the reversal of pancytopenia upon cessation of linezolid therapy without any modulation of his immunosuppression, are compelling evidence of a link between cytopenias and the use of linezolid.

Of note, patient B’s anaemia recurred quickly when linezolid and vitamin B6 therapy were started simultaneously (Figure 1b), suggesting that several weeks of vitamin B6 therapy may be required to reverse the effects of linezolid. Indeed, after the subsequent 2 week period of vitamin B6 therapy without linezolid, the linezolid was re-initiated again, and in the ensuing 7 months, there was no recurrence of the patient’s cytopenias (Figure 1b).

The peripheral neuropathy that developed in patient A also appears likely to be due to linezolid treatment. Peripheral neuropathy is not a well-described adverse effect of clarithromycin. However, linezolid has been implicated as the cause of peripheral neuropathies with similar clinical characteristics.3 These cases involved patients who had taken linezolid for more than 4 weeks, and in no patient did the neuropathy reverse following cessation of linezolid therapy. More recently, optic neuropathy associated with linezolid use has been reported to reverse following cessation of linezolid therapy, with no administration of vitamin B6.10 Hence, patients receiving long-term linezolid therapy should be closely monitored for peripheral and optic neuropathy.

In summary, we report two patients who developed linezolid-associated cytopenias, both of which improved with administration of vitamin B6, and stabilized during continued linezolid therapy. Given its low cost and negligible adverse effects, these cases suggest that prophylactic vitamin B6 treatment may represent one approach to preventing or modifying the course of cytopenias in patients receiving prolonged courses of linezolid. More formal study of this potential treatment is warranted.

## Financial disclosure

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## References


B6 reverses linezolid-induced cytopenias


