Peripheral Neuropathy Associated With Prolonged Therapy With Linezolid.

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Abstract

Linezolid is a licenced antibiotic that is useful in the treatment of certain drug resistant gram positive cocci e.g. Staphylococcal aureus infections.[1] In rare instances, prolonged therapy with Linezolid has been associated with the development of neurotoxic adverse drug reactions variably involving the central, optic, and/or peripheral nervous systems. This paper describes two cases involving older patients who developed persistent sensorimotor peripheral neuropathy following lengthy periods of treatment with oral Linezolid for chronic bone and joint prosthesis related infections respectively. Two validated causality assessment systems are applied to the index case reports as part of the pharmacovigilance process, with the aim of promoting objectivity when assessing for the likelihood that a suspected agent is the cause for a noted adverse drug reaction. The paper also briefly reviews the literature, with an emphasis on antimicrobial agents and some potential mechanisms that have been put forward for medication-associated peripheral neuropathies.

CASE 1

A 73 year old caucasian lady was admitted to hospital with clinical and radiological evidence of chronic osteomyelitis. This was associated with a lingering infection to a right proximal femoral prosthesis. Wound cultures from a discharging sinus grew multi-drug resistant Staphylococcus species.

Her medical history was notable for chronic severe depression, previous alcohol excess, urge urinary incontinence, osteoporosis, falls, and complicated right hip revision surgeries for peri-prosthetic fractures. She had been abstinent of alcohol for many months, both prior to and during the period of prolonged hospitalisation.

Her medications (all oral) on admission included Lofepramine 280mg daily, Citalopram 20mg daily, Diazepam 2mg daily, Nitrazepam 7.5mg nocte, L-Tryptophan 2 Gramme nocte, Risedronate Sodium 35mg weekly, Calcichew D3 forte - 1 tablet twice daily, Furosemide 60mg daily, extended release Oxycodone Hydrochloride 25mg twice daily, Folic Acid 5mg daily and Senna 15mg nocte.

Following orthopaedic interventions, she was treated with oral Linezolid 600mg twice daily for the persistent deep-seated bone infections. After 4 months of treatment, she described the insidious onset of painful sensations to her legs. Clinical examination noted bilateral diminished perception to light touch, joint position, vibration, and pinprick sensations below the knees. Bilateral distal lower limb muscle strength was Medical Research Council [MRC] Grade 4, with absent ankle reflexes. Upper limb sensation and motor function remained unchanged. Vision and other cranial nerves were unaffected. Digital rectal examination (DRE) was normal and perianal sensation was preserved. The earlier noted symptoms of chronic urge urinary incontinence remained unchanged.

Renal, liver and thyroid function tests were normal; as were serum vitamin B12, folic acid and glucose levels. There was a mild macrocytic anaemia with haemoglobin level of 111 g/L and mean corpuscular volume (MCV) of 100fL. White cell counts and the inflammatory marker CRP had progressively normalised during the period of prolonged antibiotic therapy. A chest x-ray was normal. Nerve conduction studies were performed, and were in keeping with an axonal sensorimotor polyneuropathy.

Less common causes of peripheral neuropathy such as amyloidosis, porphyria, vasculitis, connective tissue diseases, other toxins and heavy metals like Lead were considered, but deemed clinically unlikely.

A diagnosis was made of a peripheral neuropathy probably

arising as an adverse drug reaction (ADR) to prolonged therapy with oral Linezolid.

Symptom control for the painful neuropathy required the titrated introduction of oral Gabapentin 300mg thrice daily, in addition to the concurrent use of oral Oxycodone hydrochloride. The clinical features of peripheral neuropathy were persistent even after 6 months of withdrawal of the Linezolid.

CASE 2

An 84 year old caucasian lady was admitted to hospital with clinical signs of chronic infection in relation to a previously revised right knee replacement. She went through further knee washout procedures. Cultures grew a mixture of coagulase negative Staphylococcus aureus, Enterococcus species and Streptococcus mitis.

Her medical history was notable for previous lymphoplasmacytic lymphoma, previous pulmonary emboli, steroid associated proximal myopathy associated with previous treatment for dermatomyositis, hypertension, osteoporosis, asymptomatic gallstones, severe diverticular disease, urge urinary incontinence, and previous MRI noted degenerative disease of the lumbar spine with no significant cord or nerve root compression.

Her medications (all oral) on admission included Lansoprazole 15mg daily, Alendronic acid 70mg weekly, Atenolol 25mg daily, Atorvastatin 20mg daily, Adcal D3 – 1 tablet twice daily, Aspirin 75mg daily, Paracetamol 1 gramme four times daily, and Tramadol 50mg twice daily. She had listed allergies to penicillin, erythromycin, co-trimoxazole and streptomycin. She was teetotal and a non-smoker.

She was noted to have a chronic normocytic anaemic and chronic hyponatraemia, with Hb 74g/L, MCV 90fL, and serum sodium reached a nadir of 124 mmol/L (normal 135 – 145). She was transfused with two units of packed red cells, with post-transfusion haemoglobin 94 g/L. An upper gastrointestinal endoscopy noted Grade D oesophagitis. The severe oesophagitis was thought to be related to aspirin and bisphosphonate therapy, and both were discontinued. The hyponatraemia was thought to be related to her ongoing use of the proton pump inhibitor (PPI) Lansoprazole.[2,3] The serum sodium subsequently normalised following a change to an alternative PPI, Esomeprazole 20mg daily as replacement therapy for oesophagitis.

Following surgical interventions, the chronic infection to the prosthetic knee was initially treated with IV Vancomycin, IV Clindamycin and IV Meropenem for 2 weeks. This was subsequently modified with further Microbiology advice to oral Rifampicin 450mg twice daily for 4 weeks, followed by a course of oral Linezolid 600mg twice daily and oral Metronidazole 400mg thrice daily for a further 4 weeks.

Following the course of treatment with oral Linezolid and Metronidazole, she described the insidious onset of reduced sensation to her feet and ankles. Clinical examination showed diminished sensation to light touch, as well as to the sensations of joint position, vibration, and pinprick in her feet up to the ankle region bilaterally. Muscle strength to her lower limbs distally was MRC Grade 4. The ankle reflexes were absent. Upper limb sensation and motor function were unaffected. Cranial nerves were normal. DRE was normal and perianal sensation intact. The earlier reported symptoms of urge urinary incontinence remained the same.

Renal, liver and thyroid function tests were normal. Serum vitamin B12, folic acid and glucose levels were also normal. White cell counts and the inflammatory marker CRP normalised after the prolonged antibiotic treatments. A chest x-ray showed a small pleural effusion and an echocardiogram showed mild diastolic dysfunction. Her lymphoma was in remission and a CT scan of her chest, abdomen and pelvis did not suggest disease recurrence.

As with the first case, less common causes of peripheral neuropathy were considered, but deemed clinically unlikely.

A nerve conduction study was not performed in this case on account of the patient's frailty and attendant logistic challenges in accessing the test in another centre. However, we made a clinical diagnosis of mixed sensorimotor peripheral neuropathy arising as a possible adverse drug reaction to the concomitant therapy with oral Linezolid and Metronidazole. Both antibiotic agents were discontinued and the long term suppressive antibiotic treatment was subsequently revised to oral doxycycline 100mg daily.

The clinical features of peripheral neuropathy were persistent even after 6 months of withdrawal of the Linezolid and Metronidazole.

DISCUSSION

Linezolid: This is a synthetic oxazolidinone that has been licenced as an antibiotic.[1,4] The treatment of multi-drug resistant gram positive organisms such as Vancomycin

resistant Enterococcus spp and methicillin-resistant Staphylococcus aureus (MRSA) infections can be challenging. Linezolid has been proven to be an effective agent in the antimicrobial armoury.[1]

The recommended duration for Linezolid therapy is for periods of usually no more than 28 days.[1] Prolonged periods of treatment with Linezolid have been associated with rare neurotoxic side-effects that can variably affect the central, optic and/or peripheral nervous systems.[1, 5 - 9]

However, in certain clinical instances it is recognised that prolonged periods of treatment with antibiotics might potentially be required e.g. in deep seated infections like chronic osteomyelitis, infective discitis, prosthesis-related infections and infective endocarditis.[1, 10, 11]

A few reports have indicated significant recovery of optic neuropathy following discontinuation of Linezolid.[7, 8] In contrast, the prospects for recovery from the peripheral neuropathy associated with Linezolid therapy has been reported as being rather more unpredictable; with the condition generally being more persistent or incomplete.[6, 8]

Metronidazole: This is a 5-nitroimidazole compound and an antibiotic that has been used extensively e.g. in anaerobic and protozoal infections. Rarely, it has also been associated with peripheral neuropathies, and particularly when taken for prolonged courses.[1, 12] It is therefore plausible that the concomitant use of oral Linezolid and oral Metronidazole, as described in the second patient in this report, jointly predisposed to the development of the adverse reaction of peripheral neuropathy.

ADR Causality Assessment Systems: The application of validated causality assessment systems in the review of ADR-related case studies can potentially promote increased objectivity when ADRs are reported in association with medications, and can also support pharmacovigilance related assessments.[13-15]

Applying the Naranjo Adverse Drug Reaction Probability Scale[13] (see Table 1) to the index case reports, generates respective scores of 3 (case report 1) and 2 (case report 2), which equate to a 'Possible' ADR classification in both cases.

Figure 1

Table 1. Naranjo ADRS algorithm

1. Are there previous conclusive reports on this reaction?

   Yes (+1) *No (0) Do not know or not done (0)*

2. Did the adverse event appear after the suspected drug was given?

   Yes (+2) *No (-1) Do not know or not done (0)*

3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?

   Yes (+1) ***No (0)*** *Do not know or not done (0)*

4. Did the adverse reaction appear when the drug was readministered?

   Yes (+2) No (-2) ***Do not know or not done (0)***

5. Are there alternative causes that could have caused the reaction?

   Yes (-1) *No (+2) Do not know or not done (0)*

6. Did the reaction reappear when a placebo was given?

   Yes (-1) No (+1) ***Do not know or not done (0)***

7. Was the drug detected in any body fluid in toxic concentrations?

   Yes (+1) No (0) ***Do not know or not done (0)***

8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? *Yes (+1) No (0)* ***Do not know or not done (0)***

9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?

   Yes (+1) ***No (0)*** *Do not know or not done (0)*

10. Was the adverse event confirmed by any objective evidence?

    Yes (+1) *No (0) Do not know or not done (0)*

Derived Total Score of 3 translates to a classification of a *Possible* Adverse Drug Reaction (ADR).

- > 9 = definite ADR
- 5 - 8 = probable ADR
- 1 - 4 = possible ADR
- 0 = doubtful ADR

Applying another system, the WHO-UMC method,[14] also translates to a 'Possible' ADR classification in both of our reported cases (see Table 2).

Figure 2

Table 2. WHO-UMC Causality Categories

Causality term	Causality term Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

(WHO. The Upsalla Monitoring Centre) * All points should be reasonably complied with

Review of some possible Mechanisms of Drug-induced

Neuropathies: The pathogenesis of drug-induced neuropathies is poorly understood due to limited opportunities for histological validation of the peripheral nerves.[16] The most common neuropathologic finding associated with drug-induced neuropathies includes Wallerian degeneration, a segmental demyelination resulting in axonal loss.[17] In contrast, few drugs are thought to induce an arteritis or severe vasospasm and thereby cause ischaemic nerve damage.[16]

Examples of a range of antimicrobial agents[1, 18] associated with peripheral neuropathy include:

1] Antimycobacterial agents e.g. Isoniazid, Rifampicin, Ethambutol, Ethionamide and Cycloserine.

2] Antiparasitic agents e.g. Metronidazole and Suramin.

3] Antiviral agents e.g. Foscarnet sodium, Stavudine (d4T) Lamivudine (3TC), Zalcitabine (ddC) and Didanosine (ddI).

4] Antibacterial agents e.g. Nalidixic acid and other quinolones, Nitrofurantoin, Polymyxin B and Colistin (Polymyxin E).

Some agents (e.g. Chloramphenicol) are thought to possibly result in neuropathy by causing vitamin B12 deficiency[16] and others (e.g. Nitrofurantoin) by acting as a Folic acid antagonist. Another hypothesis for a mechanism of neurotoxicity is via Acetyl-coenzyme-A inhibition interfering with carbohydrate metabolism (e.g. Nitrofurantoin)[17]. Some other identified or suspected mechanisms are thought to involve an interference with Pyridoxine metabolism (e.g. Isoniazid), interference with Pyruvate oxidation (e.g. the Nitrofurans), and the inhibition of lipid/fatty acid metabolism (e.g. Perhexiline).[16]

There have been several hypotheses put forward regarding the mechanism of causation of Metronidazole-induced peripheral neuropathy. One theory suggests that Metronidazole or one of its metabolites probably causes peripheral axonal degeneration by binding to RNA and inhibiting neuronal protein synthesis.[19] Others have suggested that reactions with catecholamine neurotransmitters can generate some neurotoxic radicals. Within the cerebellar and vestibular systems, the intermediate metabolites of Metronidazole are suspected to modulate the receptor of the inhibitory neurotransmitter GABA.[20]

Linezolid‐induced optic neuropathies have also been described and studied previously, with some investigators postulating that sensitivity to mitochondrial dysfunction is a possible mechanism for the neurotoxicity. Linezolid is thought to inhibit bacterial protein synthesis by binding specifically to rRNA of the 50S ribosomal subunit, and thereby inhibiting the formation of the protein initiation complex. The mitochondria in mammalian nerve cells contain DNA, but their ribosomal usage is reportedly similar to that of bacterial cells, and it is thought that this ribosomal similarity could potentially make them more vulnerable to treatment with Linezolid.[21] Peripheral neuropathy has also been described in association with Linezolid-induced lactic acidosis, and this could further suggest a link with mitochondrial toxicity; with correlations drawn to possible similar mechanisms of inducing lactic acidosis and peripheral neuropathy by the nucleoside analogue related interference caused by Lamivudine.[22]

Furthermore, some investigators have proposed that identified structural and functional similarities between Linezolid and the Monoamine Oxidase Inhibitor (MAOI) class of drugs could potentially offer an explanation as to why these agents can cause neuropathies. The Linezolid associated neuropathies might represent manifest forms of an acquired mitchondrial neuropathy; and it is notable that some MAOIs (e.g. Safrazine) have also been reported to cause neuropathies.[23-25]

The medical literature shows a preponderance of anti-mycobacterial and anti-viral drugs that can cause peripheral neuropathies, with both categories representing agents that might be required for prolonged periods of treatment. This temporal association could indicate that the duration of therapy is in itself a crucial factor in the development of anti-microbial agent associated neuropathy, i.e. irrespective of the underlying pathophysiological mechanisms of its causation.

Conclusion and summary: The reporting of cases of Linezolid-associated neurotoxic side-effects in the medical literature is noted to have spanned multiple clinical specialities e.g. paediatric/adolescent medicine[5], general adult (internal) medicine[9], ophthalmology[7], orthopaedics[7] and geriatric medicine (the two index case reports). This clinical reminder is therefore of practical relevance to a wide range of clinicians. We would suggest that targeted neurological examinations are important in patients taking Linezolid, and particularly if its use is indicated beyond the usual recommended duration.

References

1. British National Formulary. Edition 62, Sept 2011. BMJ Group and Pharmaceutical Press.
2. Fort E, Laurin C, Baroudi A, Liebaert-Bories MP, Strock P. Lansoprazole-induced hyponatremia. Gastroenterol Clin Biol 2000 Jun-Jul; 24(6-7):686.
3. Ogundipe OA & Cross C. Hyponatraemia associated with the use of a proton pump inhibitor. Scott Med J 2009:54(1);58. doi: 10.1258/rsmsmj.54.1.58i
4. Quinn DK & Stern TA. Linezolid and Serotonin Syndrome. Prim Care Companion J Clin Psychiatry. 2009; 11(6): 353–356. doi: 10.4088/PCC.09r00853.
5. Linam WM, Wesselkamper K, Gerber MA. Peripheral neuropathy in an adolescent treated with linezolid. Pediatr Infect Dis J. 2009 Feb;28(2):149-51.
6. Ferry T, Ponceau B, Simon M, Issartel B, Petiot P, Boibieux A, Biron F, Chidiac C, Peyramond D. Possibly linezolid-induced peripheral and central neurotoxicity: report of four cases. Infection. 2005 Jun;33(3):151-4.
7. Saijo T, Hayashi K, Yamada H, Wakakura M. Linezolid-induced optic neuropathy. Am J Ophthalmol. 2005 Jun;139(6):1114-6.
8. Bressler AM, Zimmer SM, Gilmore JL, Somani J. Peripheral neuropathy associated with prolonged use of linezolid. Lancet Infect Dis. 2004 Aug;4(8):528-31. Comment in: Lancet Infect Dis. 2004 Aug;4(8):485.
9. Rho JP, Sia IG, Crum BA, Dekutoski MB, Trousdale RT. Linezolid-associated peripheral neuropathy. Mayo Clin Proc. 2004 Jul;79(7):927-30.
10. Talsania N & Ogundipe OA: Infective Discitis Mimicking Infective Endocarditis and Osteoarthritic Back Pain. The Internet Journal of Rheumatology. 2005 Volume 2 Number 1. Accessible on www.ispub.com.
11. Ogundipe OA & Kar-Purkayastha S. An audit of antibiotics usage and their effect on MRSA infection or colonisation following percutaneous endoscopic gastrostomy in a district general hospital. Int. J of Clin Pract. 2004;58(6): 632-634.
12. Ferroir JP, Corpechot C, Freudenreich A, Khalil A. Metronidazole-related polyneuritis, convulsive seizures, and cerebellar syndrome. Contribution of MRI. Rev Neurol (Paris). 2009 Oct;165(10):828-30.
13. Naranjo CA, Busto U, Sellers EM, et al. (1981). A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30 (2): 239–45. doi:10.1038/clpt.1981.154. PMID 7249508.
14. http://www.who-umc.org/DynPage.aspx?id=97224&mn1=7347&mn2=7252&mn3=7257 Last accessed 01.09.12
15. http://www.who-umc.org/Graphics/24734.pdf Last accessed 01.09.12
16. Zohar Argov,Frank L Mastalgia. Drug-induced peripheral neuropathies. BMJ 1979;1:663-666
17. Sharafadinzadeh N, Moghtaderi A, Alavi-Naini R. Nitrofurantoin-induced peripheral neuropathy: a lesson to be re-learnt. Neurol India. 2008 Jan-Mar;56(1):94-6.
18. Cunha BA. Antibiotic side effects. Med Clin North Am. 2001 Jan;85(1):149-85.
19. Bradley WG, Karlsson IJ, Rassol CG. Metronidazole neuropathy. BMJ. 1977 Sep 3;2(6087):610-1.
20. Puri V. Metronidazole neurotoxicity. Neurol India. 2011 Jan-Feb;59(1):4-5.
21. Javaheri M, Khurana RN, O'hearn TM, Lai MM, Sadun AA. Linezolid-induced optic neuropathy: a mitochondrial disorder? Br J Ophthalmol. 2007 Jan;91(1):111-5.
22. Apodaca AA, Rakita RM. Linezolid-induced lactic acidosis. N Engl J Med. 2003 Jan 2;348(1):86-7.
23. Sourdille MJ. Optic neuritis caused by monoamine oxidase inhibitors. Bull Soc Ophtalmol France 1964; 64: 981–88.
24. Hamada H, Saito T, Torii J. A case of optico-neuropathy due to treatment with monoamine oxidase inhibitor (safrazine). Rinsho Shinkeigaku 1979; 19: 379–87.
25. Leibold JE. Drugs having a toxic effect on the optic nerve. Int Ophthalmol Clin 1971; 11: 137–57.

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