e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(12); 541-545

Original Research Article

Linezolid Induced Peripheral Neuropathy- How Do We Treat It?

Prakash R Deshmukh[1*], Helee Khetan[2], Manjiri Ranade[3], Kailash Kothari[4], Shreyas Godbole[5]

[1]FIPP, FIAPM, D. Anaesthesiology, Spine and Pain Management Centre, Kalyan West Pain Clinic of India, Mumbai, Maharashtra, India

[2] MD, Anaesthesiology, FPCI, Khetan Pain and Spine Clinic, Gorakhpur, India

[3]FIAPM, D. Anaesthesiology, Pain Clinic of India

[4]FIAPM, MD Anaesthesiology, Pain Clinic of India

Received: 15-10-2023 / Revised: 16-11-2023 / Accepted: 14-12-2023

Corresponding author: Dr. Prakash R Deshmukh

Conflict of interest: Nil

Abstract

Background: Linezolid induced peripheral neuropathy (LIPN) is a relatively unexplored form of peripheral neuropathy which is commonly seen in the Indian population due to a higher incidence of treatment of multi-drug resistant tuberculosis. There have been a few cases described in literature, but the current guidelines for the treatment of peripheral neuropathies do not include LIPN as a subcategory while developing the treatment algorithms. As such, physicians who are the primary caregivers for these patients tend to undertreat the condition. This leads to a significant number of patients, who continue having chronic neuropathic pain that affects their day-to-day life.

Methods: 50 patients with LIPN presented to the clinic. They were being treated with low dose Gabapin NT (400/10 1 tablet OD) and had not experienced any relief in their pain. They were placed on a high dose regimen comprising of Gabapin NT (400/10) 2 tablets TDS and were called for follow up after 3 days. Patients who experienced severe side effects such as tremors or dizziness were managed by dose adjustment. Patients lost to follow-up or with incomplete data were not included for analysis.

Results: Patient data for 44 patients was available. 9 patients out of these were lost to follow up. Out of the remaining 35, 22 patients (62.85%) experienced pain relief, while 13 patients (37.14%) experienced no relief in their pain and were switched to another medication. We present the results of treating LIPN with high dose gabapentin-nortriptyline (Gabapin NT, 400mg/10mg), within the recommendations of the current guidelines for treatment of peripheral neuropathies.

Conclusion: A high dose Gabapentin-Nortriptyline combination regimen can be used with good results in patients who experienced neuropathy following chronic Linezolid use and should be brought into clinical practice. Studies that examine the treatment guidelines for LIPN must be encouraged, as this is of direct benefit in the Indian population.

Keywords: Linezolid, Neuropathy, Gabapentin, Nortriptyline, Tuberculosis.

Introduction

Linezolid is an antimicrobial used as a second line drug in the treatment for Multi-drug Resistant Tuberculosis (MDRTB). In a country like India where tuberculosis is common amongst the general population, an emerging trend of drug resistance has been noticed, with an increase in the cases of MDRTB seen in the past two decades [1]. While linezolid has been associated with the development of gastrointestinal side effects and thrombocytopenia [2], its neurologic side effects are being reported more frequently now.

The long term use of linezolid is linked to the development of optic neuropathy and peripheral neuropathy [3–5]. The cessation of linezolid is associated with a reversal of the optic neuropathy, but patients who develop peripheral neuropathy continue to experience symptoms long after the drug is withdrawn [4].

Guidelines for the management of peripheral neuropathies have been created after extensive research and continue to be updated, however, there do not exist guidelines that address drug-induced neuropathies and their treatment. In such cases, physicians tend to treat drug-induced neuropathies with a conservative approach, starting at low doses of pharmacological agents which may be otherwise ineffective at addressing patients' complains. This usually leads to undertreatment, which inevitably

affects the patient's life and leads to a high rate of dropping out of treatment cycles.

This increasing burden of drug-induced peripheral neuropathies must be addressed effectively, with an attempt to define the role pf pharmacological agents and the dose of drugs in treating the symptoms of the patients.

Here, we present a study of 50 patients diagnosed with Linezolid Induced Peripheral Neuropathy (LIPN) who were treated with different doses of gabapentinoids and their outcome.

Materials and Methods

50 patients who were undergoing treatment for MDRTB with Linezolid (600 mg once a day for four to six months, followed by 300 mg) presented to their primary care pulmonary physician with symptoms of peripheral neuropathy after four months of treatment, between March 2019 and March 2022. They were prescribed Gabapentin with Nortriptyline at a dose of 400mg/10mg once a day and asked to return for follow up if they had no relief in symptoms, or after 1 month, whichever was earlier.

The patients were referred to a higher pain management centre with a dedicated Pain Physician if their symptoms did not improve.

The referred patients were placed on a regimen of high dose Gabapentin with Nortriptyline (400/10) 2 tablets 3 times a day and asked to follow up after 3 days. Patients who developed side effects such as tremors or dizziness were managed by titrating the dose. Patients who experienced no relief from their symptoms were switched to another medication.

Patients who were lost to follow-up were excluded from the study.

Patients were administered the painDETECT Questionnaire (© Pfizer) at their first and last visits for pain assessment.

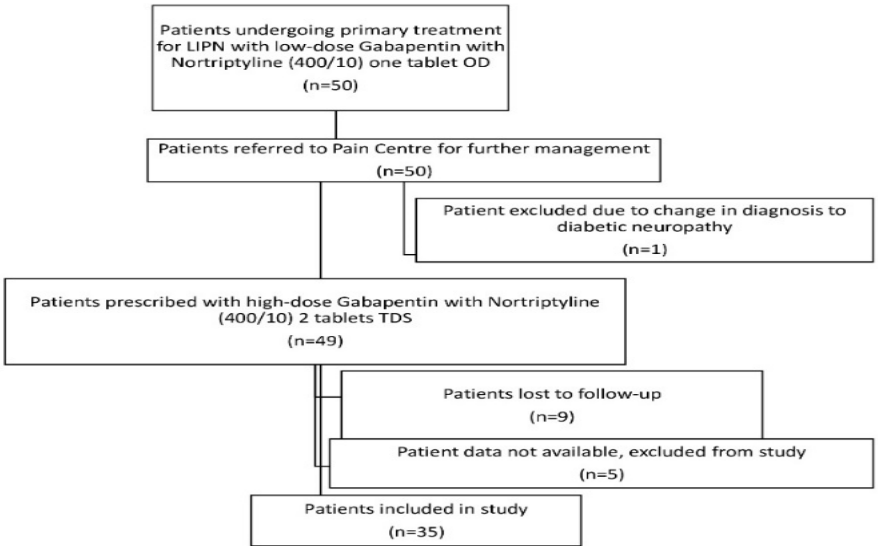

Figure 1: Methodology

Results

50 patients who were diagnosed with LIPN based on their clinical signs and symptoms were undergoing treatment with Gabapentin with Nortriptyline (400/10) 1 tablet once a day. They were referred to the Pain Centre for management of peripheral neuropathy due to non-resolution of symptoms. 1 patient from this group was excluded as the diagnosis was amended to diabetic neuropathy.

Out of the remaining 49 patients, the data for 5 patients was not available to us.

Table 1: Basic parameters

Parameter	Data
Total	44
Age (years)	30.66 ± 10.21
Gender	Female- 30 Male- 14
BMI (kg/m^2)	19.89 ± 4.83

These patients were prescribed Gabapentin with Nortriptyline (400/10) two tablets three times a day and were asked to follow-up after 3 days for assessment of change in their symptoms.

Table 2: Adverse drug reaction

Side effect	Number of patients who experienced it	Duration of treatment	Management
Giddiness	6	3 days (n=5) 1 month (n=1)	Reduction of dose to 1 TDS, then 1 BID
Fine tremors	2	3 days	Reduction of dose to 1 TDS
Sedation	1	3 days	Reduction of dose to 1 TDS
Slipping of footwear	3	2 months	
Burning in feet	1	2 months	
Tightness and swelling	2	2 months	

9 patients were lost to follow-up. Out of the remaining 35, 22 patients (62.85%) experienced pain relief, while 13 patients (37.14%) experienced no relief in their pain and were switched to another medication.

The number needed to treat (NNT) was calculated where we considered low-dose Gabapentin with Nortriptyline (400/10) as the control/placebo group, and high dose Gabapentin with Nortriptyline (400/10, 2 tablets TDS) as the experiment group. NNT was calculated to be 2 (95% CI 1.3-2.1). The absolute risk reduction (ARR) was 62.86% (95% CI 46.85% - 78.86%).

All of the patients in the study experienced a reversal of peripheral neuropathy with return to normal clinical findings at the end of treatment.

Discussion

Peripheral neuropathies are commonly encountered during a Pain Physician's practice lifetime. As the understanding of the underlying mechanisms that result in the symptoms associated with neuropathy improved, so did their management. Guidelines for the management of peripheral neuropathy are followed worldwide and the general consensus is the use of gabapentinoids, tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) as the first line drugs [6–13]. The maximum recommended dose of Gabapentin is 3600 mg/day in three divided doses [9,10] while one study has recommended a maximum dose of 1800 mg/day [6], while nortriptyline can be safely given up to 100 mg/day [9,10].

Despite there being evidence that Gabapentin is safe to use at high doses [7,14], it has been found that physicians in India tend to prescribe low doses for neuropathic pain [9,15,16]. A study published in 2020 showed that physicians did not adhere to NeuPSIG (Neuropathic Pain Special Interest Group) guidelines while managing neuropathic pain arising from cancer, with underdosing observed in a high number of patients [16]. A 2017 study had earlier found that in India, physicians treating peripheral neuropathies commonly prescribe gabapentin at initiation and maintenance doses of 100-300 mg/day, far less than the recommended 300-900 mg three times a day [6,9]. The 2017 Cochrane review also recommends that Gabapentin at doses of 1800 to 3600 mg daily provides good pain relief in postherpetic and diabetic peripheral neuropathies [17].

The one thing common in these guidelines is that there is no mention of drug-induced peripheral neuropathies as a separate category for treatment guidelines. As such, the routine treatment for peripheral neuropathies is applied to such patients. Even then, there is a high rate of undertreatment of patients. Drug-induced peripheral neuropathies are well documented in literature. It is known that antitubercular drugs, especially those used in the treatment of multi-drug resistant (MDRTB) and extremely drug-resistant tuberculosis (XDRTB) are associated with a multitude of side effects [18–20]. Amongst these, isoniazid use has been attributed to the development of peripheral neuropathy which is treated by supplementing the patient with pyridoxine (Vitamin B6) to prevent the development of neuropathy. Ethambutol is associated with optic neuropathy, but not with peripheral neuropathy. Cycloserine and para-amino salicylic acid also contribute to the development of peripheral neuropathy [18].

When Linezolid was first introduced, its side effect profile included myelosuppression [2,21]. As it was used with increasing frequency among the general population, further side effects became known. The development of peripheral neuropathy was noted with prolonged use of linezolid (beyond 28 days) by multiple centres, and several cases were reported all over the world [4]. The mechanism of nerve damage due to linezolid is not very well understood. A study published in 2016 showed that prolonged exposure of mice to linezolid was associated with small sensory fibre neuropathy [3]. In the same study, it was shown that *in vitro* exposure to linezolid cause mitochondrial dysfunction in neurons, which may be a cause for axonal damage.

A 2020 study found that 32% of patients taking low dose (<600mg) linezolid developed peripheral neuropathy confirmed by electromyographic studies, after 8 months of treatment, which was irreversible in up to 78% patients [5]. A meta-analysis showed that up to 30% of patients taking high dose linezolid (>600 mg) developed peripheral neuropathy at 2 to 4 months after treatment which was reversed in most patients following discontinuation of the drug.

The patients who were referred to the author's clinic had been diagnosed with Linezolid Induced Peripheral Neuropathy (LIPN) by their treating pulmonary physician. They had been receiving linezolid 600 mg daily followed by 300 mg after 6 months and had developed symptoms of peripheral neuropathy after 4 to 6 months of intake. As the patients belonged to an economically deficient background, nerve conduction studies were not done to confirm the diagnosis of peripheral neuropathy; the diagnosis was clinical.

Once the patients presented to the pain clinic, it was found that they had been treated with a Gabapentin-Nortriptyline combination (400/10 mg) one tablet daily. As mentioned earlier, this is a low dose regimen which has been shown to be less effective in treating neuropathies. The dose of Gabapentin-nortriptyline (400/10 mg) was increased to 2 tablets three times a day (2400 mg gabapentin and 60 mg nortriptyline per day). This is in line with the existing guidelines for treatment of peripheral neuropathies [6–13]. 63% of our patients experienced relief from symptoms, with 37% patients needing to be switched to other medications. All the patients who experienced pain relief showed a complete reversal of neuropathy at 6 months after treatment. The painDETECT questionnaire was used for documenting the pain during the course of treatment of patients. It was administered by a staff member in the waiting area of the clinic, and answers were recorded. We preferred this questionnaire as it is available in vernacular languages.

The commonest side effect experienced by patients was giddiness (seen in 17%) which was managed by reducing the dose of gabapentin-nortriptyline (400/10 mg) to 1 tablet three times a day (gabapentin 1200 mg and nortriptyline 30 mg) or 1 tablet twice a day (gabapentin 800 mg and nortriptyline 20 mg). Giddiness and sedation are known side effects of gabapentinoids and tricyclic antidepressants and disappear once the drug is discontinued.

To this study, we tried to compare the low dose gabapentin-nortriptyline regimen with the high dose one, and when we calculated the number needed to treat between the two groups, it was found that the absolute risk reduction was 62.86%, and NNT was 2. This indicates that the high dose treatment is more effective for the treatment of LIPN when compared to low dose treatment.

One of the causes for the prescription of low dose regimen in the treatment of drug-induced (specifically Linezolid induced) peripheral neuropathies may be the lack of awareness amongst physicians due to no current guidelines for the same. Kamble et al published a survey in 2017 conducted among Indian doctors regarding the prescription of medications for neuropathic pain, and found that doctors in India tend to prefer low dose regimens as most of the patients treated responded well to the treatment with a less incidence of side effects [15]. There have been studies that have reported good results of low dose gabapentin therapy (300 mg/day) in non-neuropathic pain [15,22–24], but to extrapolate those findings on to patients with neuropathic pain, especially when guidelines that recommend higher doses of gabapentin are clearly defined, would be a folly.

Our study is limited by a low sample size, inability to confirm the diagnosis of LIPN due to financial constraints and erratic follow up of patients. We would recommend a study with larger sample size to be done in patients after an established diagnosis of LIPN.

Conclusion

High-dose gabapentin-nortriptyline combination is effective in the treatment of linezolid induced peripheral neuropathy. Further studies with higher number of patients are needed to establish a guideline for the treatment of LIPN, as it is more commonly encountered due to a rise in cases of MDRTB treated with Linezolid.

References

1. Paul R. The Threat of Multidrug-resistant Tuberculosis. J Glob Infect Dis 2018; 10:119–20.
2. Birmingham MC, Rayner CR, Meagher AK, Flavin SM, Batts DH, Schentag JJ. Linezolid for the treatment of multidrug-resistant, gram-positive infections: experience from a compassionate-use program. Clin Infect Dis Off Publ Infect Dis Soc Am 2003; 36:159–68.
3. Bobylev I, Maru H, Joshi AR, Lehmann HC. Toxicity to sensory neurons and Schwann cells in experimental linezolid-induced peripheral neuropathy. J Antimicrob Chemother 2016; 71:685–91.
4. Bressler AM, Zimmer SM, Gilmore JL, Somani J. Peripheral neuropathy associated with prolonged use of linezolid. Lancet Infect Dis 2004; 4:528–31.
5. Jaspard M, Butel N, El Helali N, Marigot-Outtandy D, Guillot H, Peytavin G, et al. Linezolid-Associated Neurologic Adverse Events in Patients with Multidrug-Resistant

Tuberculosis, France. Emerg Infect Dis 2020; 26:1792–800.
6. Saxena AK, Jain P, Dureja GP, Venkitachalam A, Goswami S, Usmani H, et al. Pharmacolo gical management of neuropathic pain in India: A consensus statement from Indian experts. Indian J Pain 2018; 32:132.
7. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015; 14:162–73.
8. Moisset X, Bouhassira D, Avez Couturier J, Alchaar H, Conradi S, Delmotte MH, et al. Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations. Rev Neu rol (Paris) 2020; 176:325–52.
9. Dureja GP, Iyer RN, Das G, Ahdal J, Narang P. Evidence and consensus recommendations for the pharmacological management of pain in India. J Pain Res 2017; 10:709–36.
10. Bates D, Schultheis BC, Hanes MC, Jolly SM, Chakravarthy KV, Deer TR, et al. A Comprehensive Algorithm for Management of Neuropathic Pain. Pain Med 2019;20: S2–12.
11. Murnion BP. Neuropathic pain: current definition and review of drug treatment n.d. https://doi.org/10.18773/austprescr.2018.022.
12. [12] Bussa M, Mascaro A, Sbacchi E, Dourandish M, Rinaldi S. Understanding peripheral neuropathic pain in primary care: diagnosis and management n.d.:7.
13. Neuropathic pain in adults: pharmacological management in non-specialist settings 2020:37
14. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118:289–305.
15. Kamble SV, Motlekar SA, D'souza LL, Kudrigikar VN, Rao SE. Low doses of amitriptyline, pregabalin, and gabapentin are preferred for management of neuropathic pain in India: is there a need for revisiting dosing recommendations? Korean J Pain 2017;30:183 –91.
16. Singh VK, Shetty YC, Salins N, Jain P. Prescription Pattern of Drugs Used for Neuropathic Pain and Adherence to NeuPSIG Guidelines in Cancer. Indian J Palliat Care 20 20;26:13–8.
17. Gabapentin for chronic neuropathic pain in adults n.d. https://doi.org/10.1002/14651858. CD007938.pub4.
18. Saroha D, Garg D, Singh AK, Dhamija RK. Irreversible neuropathy in extremely-drug resistant tuberculosis: An unfortunate clinical conundrum. Indian J Tuberc 2020; 67:389–92.
19. Cunha BA. ANTIBIOTIC SIDE EFFECTS. Med Clin North Am 2001; 85:149–85.
20. Vilholm OJ, Christensen AA, Zedan AH, Itani M. Drug-Induced Peripheral Neuropathy. Basic Clin Pharmacol Toxicol 2014; 115:185–92.
21. Peripheral neuropathy associated with prolonged use of linezolid. Lancet Infect Dis 2004; 4:528–31.
22. Khurana G, Jindal P, Sharma JP, Bansal KK. Postoperative pain and long-term functional outcome after administration of gabapentin and pregabalin in patients undergoing spinal surgery. Spine 2014;39: E363-368.
23. Grice GR, Mertens MK. Gabapentin as a potential option for treatment of sciatica. Pharmacotherapy 2008; 28:397–402.
24. Arai Y-CP, Matsubara T, Shimo K, Suetomi K, Nishihara M, Ushida T, et al. Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine. J Anesth 2010; 24:407–10.