Review Article

Linezolid Optic Neuropathy

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Abstract

Various systemic antimicrobials have been known to cause ocular adverse effects. Linezolid has been shown to be effective in treating multidrug-resistant tuberculosis. However, the related side effects, such as ocular and peripheral neuropathy, discontinue long-term treatment. In a developing country like India, where there is an increasing burden of multidrug-resistant tuberculosis, ophthalmologists and physicians should be aware of linezolid-induced optic neuropathy so that monitoring of visual functions in patients on long-term linezolid treatment can be done to avoid serious neurological consequences.

Keywords: Linezolid, Optic neuropathy, Scotoma.

Introduction

Linezolid was introduced as the first member of the new oxazolidinone synthetic group of antibiotics in the year 2000 with activity against many important pathogens, which includes multidrug-resistant tubercle bacillus, methicillin-resistant *Staphylococcus aureus* (MRSA) and streptococcus. Since then, the drug has gained widespread usage.

Uses of the Drug

It is mainly efficacious in the treatment of mycobacterial infections, including multidrug-resistant tuberculosis (MDR-TB is tuberculosis, which is resistant to isoniazid and rifampicin).[1] It is also used in the management of MRSA, vancomycin-resistant enterococcus, nosocomial pneumonia, joint infections and complicated skin infections.

Many recent studies have also shown the excellent posterior segment ocular penetration of linezolid, reaching inhibitory concentrations above the minimum inhibitory concentrations (MIC) for most of gram-positive organisms within 4 hours after a single oral dose of 600 mg in both vitreous and aqueous samples.[2]

Mechanism of Action

Linezolid inhibits protein synthesis via specific binding to 23S rRNA of the 50S ribosomal component, inhibiting the viable initiation complex formation and inhibiting bacterial protein synthesis.[3] Ribosomes in mammalian cells lack the 50S subunit; thus, linezolid produces very little effect on normal mammalian protein synthesis. Unfortunately, human mitochondria remain vulnerable as they contain DNA and use ribosomes that more closely approximate that of bacteria.[4-6] Long-term use of linezolid interferes with bacterial ribosomes and possibly human mitochondrial ribosomes, and thereby disrupting protein synthesis.

This overall process mimics the respiratory chain dysfunction usually seen in mitochondrial optic neuropathies and produces similar optic neuropathy, such as that seen in patients with Leber's hereditary optic neuropathy (LHON).

Linezolid is a well-tolerated drug with short-duration treatment with few adverse effects. It shows maximal oral bioavailability and large tissue distribution.[7] Therefore it is a very useful option when it is possible to switch from intravenous therapy (with linezolid or another drug like vancomycin) to oral treatment to reduce the duration and cost of the hospitalization or to avoid vancomycin-related renal toxicity.

Oral linezolid absorption is extensive and oxidation creates two metabolic products, the accumulation of which has unknown clinical effects. Similar pharmacokinetics are

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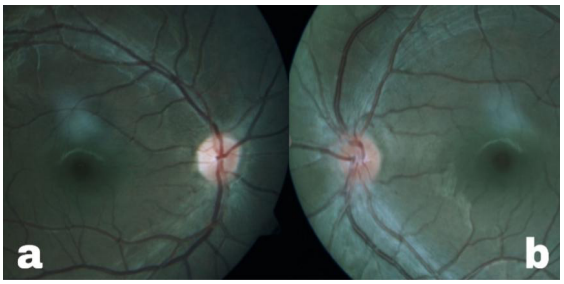


Figure 1: Fundus photograph of a patient of linezolid optic neuropathy showing disc edema (A) in right eye and (B) in left eye after using linezolid for a year

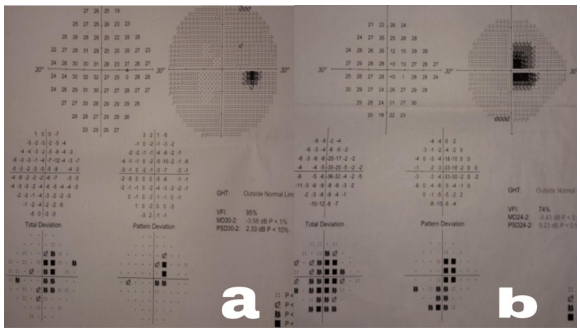


Figure 2: Visual field of the same patient as Figure 1 showing centrocecal scotoma (A) in right eye and (B) central scotoma in left eye

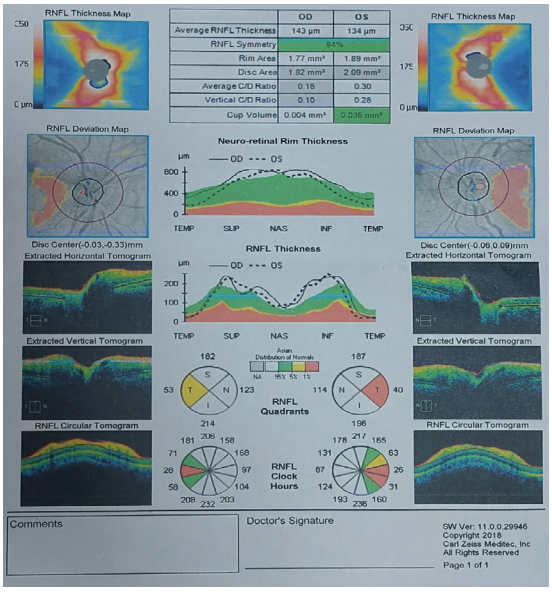


Figure 3: Stratus OCT of the same patient as Figure 1 showing an increase in retinal nerve fiber layer thickness in both eyes

seen in adult and old-age patients, so the same dosage is recommended for both populations.

However, linezolid treatment safety has been established for use only up to 28 days. Serious adverse reactions demanding withdrawal of the drug mainly includes myelosuppression peripheral and optic neuropathy.[8,9] There are many case reports of optic or peripheral neuropathy

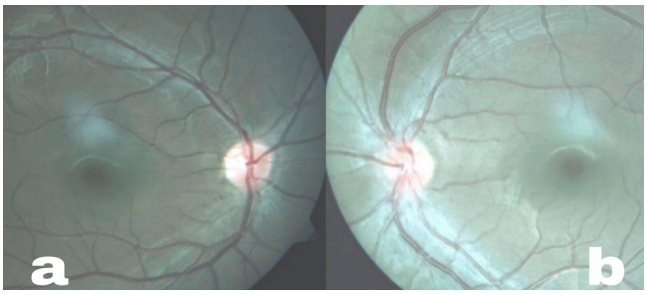


Figure 4 (A and B): Follow-up fundus photograph of the same patient showing improvement in disc edema and temporal disc pallor in both eyes

induced by linezolid in patients treated for a time period beyond 28 days.[10]

Clinical Presentation

The usual presentation is painless, gradual progressive decrease of vision in both eyes. The patient's medical history includes linezolid use either alone or in combination with some other drug in the dose of 600 mg BD or greater for a duration of greater than 28 days.

Diagnosis

On ocular examination, visual acuity is decreased in both eyes. Color vision is usually defective. Anterior segment examination is generally unremarkable and pupils are of normal size, round, regular, and reacting to light in both eyes (Direct and Indirect). There is no relative afferent pupillary defect (RAPD).

Fundus examination usually reveals a hyperemic disc with blurred margins (OU) (Figures 1a and b). Disc pallor can be seen with a longer duration of drug use. Visual field examination (by Humphrey field analyzer) usually reveals a central or centrocecal scotoma (Figures 2a and b). Peripheral constriction of fields and quadrantanopia are the other type of field defects seen. Optical coherence tomography (OCT) usually reveals an increase in retinal nerve fiber layer (RNFL) thickness (Figure 3).

Diagnosis of linezolid optic neuropathy is confirmed when there is rapid improvement in visual acuity after linezolid discontinuation. Color vision usually gets restored to normal and vision gets restored to 20/20 after approximately one month of withdrawal of linezolid in our patient of linezolid optic neuropathy (Figures 1, 2 and 3). On follow up of the same patient, fundus examination showed resolved optic disc edema with setting in of temporal pallor (Figures 4a and b). On follow-up, the visual field showed the disappearance of scotoma in both eyes (Figures 5a and b) and OCT demonstrated improvement in RNFL thickness in both eyes (Figure 6).

Workup and Investigations

A detailed medical history and careful eye examination mainly establish the diagnosis of linezolid optic neuropathy. Ocular examination for evaluation of linezolid optic

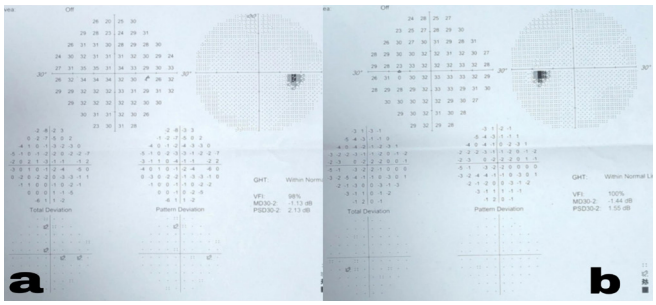


Figure 5 (A and B): Follow-up visual field showing the disappearance of scotoma in both eyes

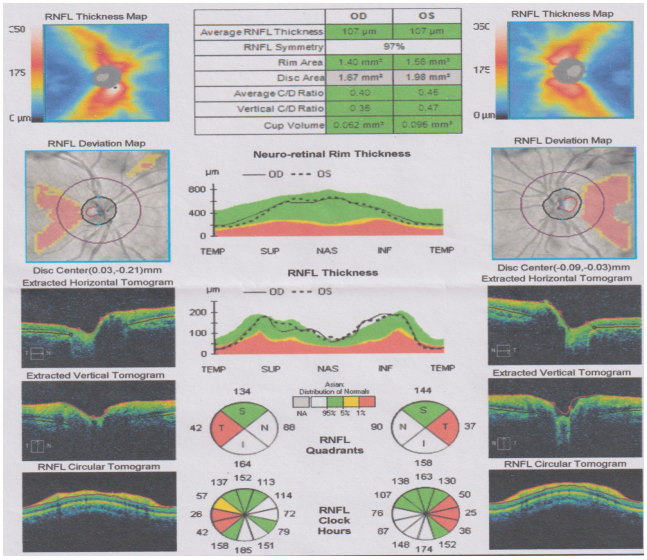


Figure 6: Follow-up stratus OCT showing improvement in retinal nerve fiber layer thickness in both eyes

neuropathy includes visual acuity, color vision, pupils, and fundus examination. OCT and visual field testing are also done. The physical examination includes blood investigations like complete hemogram, differential and total blood cell counts and urinalysis. Neuroimaging (MRI brain and orbit) is done mainly to rule out neurological lesions in case of doubt.

Management

Linezolid is usually a well-tolerated drug with few described adverse effects. Serious adverse reactions that demand withdrawal of the linezolid include optic neuropathy, myelosuppression, peripheral neuropathy, serotonin syndrome and lactic acidosis.[8] So it is important to monitor visual acuity and color vision in patients using the drug, especially if it is used longer.

The initial and main management of linezolid optic neuropathy is withdrawal of the drug, the same as with any other toxic neuropathy. Vitamin supplementation may be given. Patients should be observed initially every 4-6 weeks and then every 6-12 months, depending on their recovery. The patient's visual acuity, color vision, pupils, optic nerves, and visual fields should be assessed at each visit.

Prognosis

The visual prognosis of linezolid optic neuropathy is good in the majority of the cases.[11] Vision gradually recovers to normal over a few weeks, though it may take months for complete recovery and there is always the risk of permanent residual vision deficit.[12] Steroids have been shown to cause improvement in a few studies.[13]

Ophthalmologists and physicians must be aware that visual function monitoring is very important in patients on long-term linezolid therapy and that early observation of toxicity and drug discontinuation will result in complete visual recovery.

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