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Effectiveness of Pyridoxine and Pyridostigmine in the Treatment of Vincristine-Induced Bilateral Ptosis and External Ophthalmoplegia: A Case Report

Vinkristine Bağlı Bilateral Ptosis ve Eksternal Oftalmopleji Tedavisinde Pridoksin ve Pridostigmin Etkinliği: Olgu Sunumu

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Summary

In this manuscript, we present the case of a patient with acute lymphoblastic leukemia who developed vincristine-induced bilateral ptosis and external ophthalmoplegia and who was treated successfully with pyridoxine and pyridostigmine. Pyridostigmine and pyridoxine are promising treatment option in cases of vincristine-induced neuropathy. (Turk J Ophthalmol 2014; 44: 330-1)

Key Words: External ophtalmoplegia, ptosis, pyridoxine, pyridostigmine

Özet

Vinkristine bağlı bilateral ptosis ve ekstarnal oftalmopleji gelişen akut lenfoblastik lösemili vakada başarılı pridoksin ve pridostigmin tedavisini sunmayı amaçladık. Vinkristine bağlı nöropati iyileşmesinde pridostigmin ve pridoksin umut verici tedavi seçeneğidir. (Turk J Ophthalmol 2014; 44: 330-1)

Anahtar Kelimeler: Eksternal oftalmopleji, ptosis, pridoksin, pridostigmin

Introduction

Vincristine is a vinca alkaloid used in combination with other agents, usually in the treatment of pediatric malignancies, including acute lymphoblastic leukemia (ALL). The dose-limiting side effect of vincristine is peripheral neurotoxicity. As vincristine does not cross the blood-brain barrier in significant amounts, central nervous system toxicity is not a concern.[1] Oculomotor, trochlear, and facial nerve involvements are uncommon, but may develop unilaterally or bilaterally.[2,3] In this case report, we present full recovery of vincristine-associated bilateral ptosis and external ophthalmoplegia after treatment with pyridoxine and pyridostigmine.

Case Report

An eleven-year-old boy with ALL was started on treatment according to the GPOH-HD 95 protocol. The patient received vincristine as a part of the etoposide, doxorubicin, and prednisone (OEPA) regimen. On the 30th day of therapy, when the cumulative dose of vincristine was 6.35 mg, he developed bilateral ptosis and external ophthalmoplegia (Figure 1; permission to use images was obtained from the patient's legal guardians). Pupillary and corneal reflexes were preserved.

To make a definitive diagnosis of a drug-induced neuropathy, all other etiologies that may produce a similar clinical presentation were excluded. A possible intraocular or intracranial metastasis was ruled out by cranial and orbital magnetic resonance imaging. There were no previous clinical symptoms of neuropathy, and there was no history of inherited neuropathies or intake of any other drugs known to be neurotoxic. Neurologic examination, cerebrospinal fluid analysis, and serum electrolyte levels were all normal. After evaluating the clinical features and laboratory results, the patient was diagnosed with vincristine-induced cranial neuropathy. Vincristine treatment was discontinued, and he was put on pyridostigmine (60 mg, twice daily) and pyridoxine (150 mg, twice daily). Bilateral ptosis and extraocular muscle weakness showed clear improvement after 10 days of pyridoxine and pyridostigmine treatment. Ptosis completely resolved after three weeks (Figure 2). After complete recovery from ptosis and external ophthalmoplegia, vincristine was

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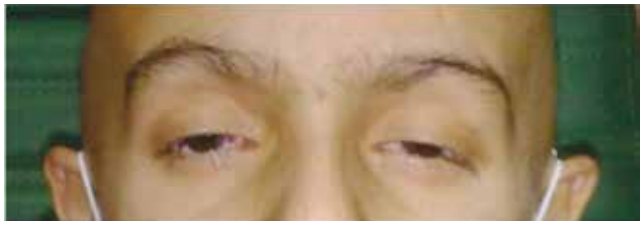

Figure 1. Vincristine-induced bilateral ptosis and external ophthalmoplegia

Figure 2. Recovery after pyridoxine and pyridostigmine treatment

reinitiated at a lower dose to resume the treatment of ALL. There was no recurrence of neuropathy in the follow-up period.

Discussion

Vincristine is a vinca alkaloid, which arrests the cell at the metaphase by inhibiting microtubules. Disruption of microtubule function leads to cell-cycle arrest and tumor cell death. However, microtubule function also has a critical role in neuronal function.[4] First generation vinca alkaloids (vincristine) are associated with more severe neuropathy than the newer vinca alkaloids (vinorelbine, vinflunine).[5]

Vincristine-associated peripheral neuropathy is a well-described phenomenon. The pathogenesis of neuropathy is explained by structural changes in the microtubules of peripheral nerves and interference with axoplasmic transport.[6] The severity of vincristine neurotoxicity increases with higher dosage, patient hypersensitivity to vincristine, pre-existing liver dysfunction, and concomitant use of other metabolism-inhibiting drugs such as allopurinol, erythromycin, isoniazid, phenytoin, or itraconazole.[3,5,7]

Anti-cancer drugs such as vincristine, paclitaxel, cisplatin, and bortezomib are well-known agents related to neurotoxicity.[4] The only risk factor for neurotoxicity in the present case was the use of vincristine. All other etiologies that may cause similar symptoms were excluded.

Pyridostigmine is a synthetic quaternary ammonium agent which increases the concentration of endogenous acetylcholine by inhibiting acetylcholinesterase. Accumulation of acetylcholine in the neuromuscular junction increases muscle strength. The primary therapeutic uses of pyridostigmine are to treat diseases of the gastrointestinal and urinary tracts (postoperative atony, neurogenic bladder), and the neuromuscular junction (myasthenia gravis, curare-induced neuromuscular paralysis).

Pyridoxine, or vitamin B6, is an essential cofactor in various transamination, decarboxylation, and neurotransmitter metabolism processes. The deficiency of pyridoxine usually causes neuropathy. Neurotransmitters like dopamine, serotonin, epinephrine, norepinephrine, glycine, glutamate, and gamma-aminobutyric acid require pyridoxine for their production. For this reason, pyridoxine is a standard component of treatment protocols for most neurodegenerative diseases.

There are three methods for treating vincristine-related neuropathy: reduction of vincristine dose; discontinuation of vincristine; and/or treatment with pyridoxine and pyridostigmine. Orhan et al.[8] reported complete recovery from mild unilateral ptosis six weeks after discontinuation of vincristine. Batta et al.[9] showed that reducing the dose of vincristine by one third resulted in the resolution of unilateral ptosis in 78 days. Müler et al.[10] reported a case of vincristine-induced bilateral ptosis which improved dramatically within one week of discontinuing vincristine and treating with pyridostigmine and pyridoxine. In another published case, similar to the present case, in which bilateral ptosis with ocular muscle involvement developed in response to a cumulative dose of vincristine, symptoms improved over a three-week treatment course of pyridostigmine and pyridoxine.[11]

The pathophysiology of vincristine neuropathy is not exactly understood; therefore, preventive and therapeutic approaches are still experimental. Pyridoxine and pyridostigmine may be useful in the treatment of neuropathy due to vincristine.

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