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The Beneficial Effects of a Combination Therapy of Oral Benfotiamine and Methylcobalamin in the Treatment of Parkinson's Disease: Case Reports and Review of the Literature

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ABSTRACT

Evidence suggests that there may be an association between Parkinson's disease (PD) and aberrations in thiamine (vitamin B1) utilization and processing. Low free thiamine levels have been found in the cerebrospinal fluid of patients with PD. Two independent research groups have reported improved symptomatology in patients with PD following high-dose parenteral thiamine therapy. Experimental models further support this connection. Benfotiamine, a lipid-soluble thiamine derivative with enhanced oral bioavailability, along with methylcobalamin, an active form of vitamin B12, have demonstrated neuroprotective properties. Here we describe two cases of patients with PD who experienced marked improvements in tremor, fatigue, cognition, and overall quality of life following oral treatment with benfotiamine and methylcobalamin.

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by tremors, rigidity, bradykinesia, and postural instability. Additionally, patients with PD may develop nonmotor symptoms, such as cognitive decline, depression, anosmia, constipation, sleep problems, and autonomic nervous system symptoms.[1] The primary pathology in patients with PD is believed to be the loss of the pigmented cells of the substantia nigra (SN) pars compacta and the dopaminergic neurons of the striatum. This results in diminished quantities of the neurotransmitter dopamine in the midbrain.[2] Recent work indicates that the misfolding of alpha-synuclein and its aggregation into Lewy bodies in the cells of the SN are also a hallmark of the disease.[3]

Thiamine (vitamin B1) deficiency (TD) is associated with several neurodegenerative diseases.[4] Thiamine regulates multiple enzymes of the Krebs cycle, including succinate thiokinase, succinate dehydrogenase, malic dehydrogenase, and the α-ketoglutarate dehydrogenase complex (KGDHC).[5] Thiamine is essential for proper intraneuronal energy production in the form of adenosine triphosphate (ATP) via mitochondrial oxidative phosphorylation. TD reduces the activity of multiple Krebs cycle enzymes. Decreased Krebs cycle activity reduces ATP production and has emerged as a likely mechanism in neurodegeneration.[6] Other mechanisms by which TD is believed to likely exert neurodegenerative effects include increased oxidative stress, increased endoplasmic reticulum stress, and impaired autophagy in the brain.[4]

Thiamine deficiency or its impaired utilization have been found in many neurodegenerative diseases. Thiamine deficiency is associated with diabetes and alcoholic use disorder-both of which may result in polyneuropathy, a neurodegenerative disease of the peripheral nervous system.[7-10] Wernicke encephalopathy (WE), a neurodegenerative disease of the central nervous system, is also associated with TD.[11] Reduced activities of thiamine-dependent enzymes have been found in the brains of patients with Alzheimer's disease (AD).[12] Impaired thiamine metabolism, in which there is defective activity of enzymes involved in the conversion of free thiamine into its phosphorylated bioactive forms, has been found to be associated with PD and amyotrophic lateral sclerosis (ALS).[13] Decreased thiamine diphosphate levels have been found in the brains of patients with frontotemporal dementia (FTD).[14] Studies indicate that abnormal thiamine processes may have a role in the pathogenesis of Huntington's disease (HD).[15]

Benfotiamine is a safe, orally administered, lipid-soluble thiamine derivative with better bioavailability than thiamine.[16] Benfotiamine is absorbed significantly better than water-soluble thiamine-delivering maximum plasma levels of thiamine about five times as high as those achieved with equivalent doses of water-soluble thiamine.[17] Benfotiamine 300 mg qd has been shown to raise thiamine levels to a greater extent than 150 mg twice a week of parenterally administered thiamine.[18] Benfotiamine has been shown to have anti-inflammatory, antioxidant, and neuroprotective properties.[19]

Benfotiamine has been shown to improve brain function in animal studies. In the brain of a rat model of neurodegeneration, it increased thiamine diphosphate levels, decreased inflammation, and reversed impairment in cognitive function.[20] In in vitro experiments on a rat model of neurodegeneration, benfotiamine increased insulin sensitivity in hypothalamic neurons.[21] Pan, et al. found in a mouse model of AD that benfotiamine reduced both amyloid plaque and phosphorylated tau levels in cortical areas of the brain. They speculated that benfotiamine most likely exerts its beneficial effects through thiamine-independent pathways.[16] Tapias, et al. found chronic dietary treatment with benfotiamine was neuroprotective, increased lifespan, improved behavior, reduced glycated tau, decreased neurofibrillary tangles, and prevented death of motor neurons in a mouse model of tauopathy.[22] They also found that treating wild-type mice with benfotiamine significantly elevated thiamine and thiamine monophosphate levels in the cerebral cortex and hippocampus. In C57BL6/J mice, benfotiamine treatment induced a modest increase in the brain content of free thiamine while the level of thiamine diphosphate remained unchanged.[23] In a rat model of PD, benfotiamine was reported to ameliorate disorders in behavior, body balance, and dopamine levels in the mid-brain.[24]

Thiamine therapy, either via parenteral administration or orally with benfotiamine or other oral forms of thiamine, has shown promise as a treatment for many neurodegenerative diseases in humans. Both diabetic and alcoholic polyneuropathies have been shown to improve with the supplementation of benfotiamine.[9,10] Thiamine supplementation is the cornerstone of the treatment of WE.[11] In 2023, Mann reported a case in which benfotiamine and methylcobalamin may have positively impacted the symptoms of a patient with ALS.[25] Benfotiamine has shown promise in the treatment of AD. Pan, et al. reported long-term cognitive improvement in five patients with mild to moderate AD who received oral benfotiamine (300 mg daily) over 18 months.[26] Gibson, et al. published their work on treating AD with benfotiamine 300 mg bid versus placebo. They found cognitive decline as measured by the Alzheimer's Disease Assessment Scale-Cognitive Subscale was 43% lower in the benfotiamine group than in the placebo group, indicating less cognitive decline. They also found that worsening in clinical dementia rating score was 77% lower in the benfotiamine group than in the placebo group, although their results did not reach statistical significance.[27] Pavlović reported that three patients with severe AD significantly improved their Mini-Mental State Examination scores after three months of benfotiamine administration (150-300 mg daily).[28]

High-dose parenteral thiamine has shown great promise as an adjunctive treatment for PD. In 2012, Luong and Nguyen reported the results of their use of high-dose thiamine administered parentally in the treatment of PD.[2] The following excerpts are from their pioneering paper, *The Beneficial Role of Thiamine in Parkinson's Disease-Preliminary Report.*

"Five PD patients presented with stone face, right-hand tremors, Parkinsonian gait and bradykinesia with

occasional freezing. Two patients presented with sialorrhea and the plasma transketolase activity was low in one patient. All of the patients received 100 - 200 mg daily doses of parenteral thiamine. Within days of thiamine treatment, the patients had smiles on their faces, walked normally with longer steps, increased their arm swings, and experienced no tremors or sialorrhea. Three patients did not require carbidopa and levodopa without effects on their movements."

From 2013 to 2019, Antonio Costantini, et al. reported treating over 2,500 people suffering from PD with parenteral high-dose vitamin B1 (100 mg twice a week) in their clinic in Italy. They published three papers on the results of their treatment of these patients. In 2013, they reported considerable improvement in three patients in the motor part of the Unified Parkinson's Disease Rating Scale ranging from 31.3% to 77.3%.[29] In 2015, they reported on the results of an open-label pilot study of 50 patients. Their treatment significantly improved motor and nonmotor symptoms within three months and remained stable.[30] In 2016, they reported on the results of an open-label pilot study in which significant improvement was noted in 10 patients.[31] Additionally, Costantini, et al. published papers documenting their successful treatment with parenterally administered high-dose vitamin B1 on patients with Friedrich's ataxia, multiple sclerosis, spinal cerebella ataxia, stroke, dystonia, and other neurodegenerative diseases.[32-36]

Here, we present two cases of patients with PD whose clinical symptoms improved when given a combination of oral benfotiamine with methylcobalamin. In each case, after consent was obtained, the patient took as a loading dose for the first 30 days capsules containing benfotiamine 300 mg and methylcobalamin 1 mg twice daily. After the first 30 days the patient took capsules containing benfotiamine 300 mg and methylcobalamin 1 mg once a day thereafter as a maintenance dose.

Case Presentation

CASE 1:

N.H. is a 64-year-old male, divorced business executive, who was diagnosed with PD in 2023 by his neurologist. The patient's past medical history is unremarkable. Family history reveals that his mother was diagnosed with PD. The patient claims that his initial symptoms were tremors in his left hand which started five years preceding the diagnosis of PD. According to the patient, he has experienced an increase in the severity and frequency of the left-hand tremors, a slight tremor in his right hand, gait imbalance, and memory loss since his diagnosis. The patient has not taken any medication for PD. His physician recommended he start taking a formulation of benfotiamine 300 mg and methylcobalamin 1 mg capsules twice daily with food for 30 days and then once a day thereafter. The patient claimed that three weeks after initiating this treatment regimen he noticed improvement in his memory and left-hand tremor. After twelve weeks, the patient claimed that his tremors had improved significantly, as had his mental clarity and sleep quality.

CASE 2:

D.M. is a 72-year-old female, single, retired U.S. government executive who was diagnosed with PD in January 2023 by her neurologist. The patient's past medical history and family history are unremarkable. The patient stated that her initial symptoms were of gradual onset, consisting of right-hand tremors, absence of a sense of smell, bilateral foot pain, curling of the toes of her right foot, severe fatigue, and difficulty getting out of a chair. Moreover, the patient stated that due to her severe fatigue, she was compelled to take daily long afternoon naps. To manage her PD, her neurologist prescribed the standard carbidopa/levodopa regimen, which provided minimal benefit. In June 2023, she started a formulation of benfotiamine 300 mg and methylcobalamin 1 mg capsules twice daily with food for 30 days and then once a day thereafter. After one week, she said she had "regained my energy, and I no longer needed to take my afternoon naps." Additionally, around month three, after taking the nutrient formulation, she claimed her hand tremors decreased by 90%.

Discussion

There appears to be a relationship between vitamin B12 and the symptoms experienced by patients with PD. In a meta-analytical assessment of the scientific literature, pooled data from 10 eligible studies indicated that patients with PD had lower vitamin B12 levels than controls.[37] Higher levels of serum vitamin B12 at PD diagnosis were noted to correlate with a lower risk of future dementia.[38] In a C. *elegans* model of PD, vitamin B12 mitigated motor dysfunction. In a mouse model of PD, vitamin B12 displayed protective effects, including the rescue of mitochondrial function, dopaminergic neuron loss, and movement disorder.[39] In a study of early PD, low vitamin B12 status was found to be common and low vitamin B12 at baseline predicted more significant worsening of mobility.[40]

A relationship between thiamine, its impaired utilization, and PD has been suggested by the work of many researchers. Mizuno reported decreased levels of KGDHC in the SN of patients with PD and that the extent of the decrease roughly correlated with the degree of severity of the disease.[41] Thiamine deficiency induced by the thiamine blocker pyrithiamine was shown to reduce KGDHC activity by 40% in the brains of rats.[42] Thiamine diphosphate (TDP), the active form of thiamine, is a coenzyme to KGDHC, the rate limiting enzyme of the Krebs cycle. As such, its deficiency impairs mitochondrial oxidative phosphorylation and energy production. Impaired thiamine utilization decreases intraneuronal energy availability-promoting neuronal death. This is particularly significant in the dopaminergic neurons of the SN, which, due to their high metabolic activity, have increased energy needs as compared to other neurons. This likely makes them more susceptible to mitochondrial dysfunction and, eventually, cell death as compared to other neurons.[6] Decreased striatal dopamine concentrations are found when vitamin B1 is deficient.[43] Rats treated with a thiamine-deficient diet were reported

to have decreased dopamine concentration in the striatum.[44] Decreased levels of dopamine metabolites were observed in an animal experimental study of thiamine deficiency.[45] Jimenez-Jimenez, et al. found patients with PD to have low free thiamine levels in the cerebral spinal fluid (CSF) and that PD patients under levodopa therapy had higher CSF levels of TDP and total thiamine than those not treated with this drug.[46] Intrastriatal administration of thiamine triphosphate (TTP) or TDP was reported to have induced dopamine release in rat striatum.[47] Laforenza, et al. found that homogenates from the frontal cortex of deceased PD patients showed significantly lower levels of thiamin-pyrophosphatase, an essential enzyme in normal thiamine metabolism.[13] Low dietary vitamin B1 intake two to eight years before diagnosing PD was found to be associated with olfactory dysfunction, a non-motor symptom related to increased risk of PD. Håglin, et al. found low plasma thiamine in male patients with PD was associated with mild cognitive impairment and low thiamin and folate density in the diet, 2-8 years before PD diagnosis, was significantly associated with olfactory dysfunction at the time of PD diagnosis.[48,49] Alizadeh, et al. reported that patients with PD had lower dietary intake of thiamine than controls and that high intake correlated with reduced odds of PD.[50] Brandis, et al. showed in a fission yeast model that high levels of thiamine suppressed alpha-synuclein aggregation, a hallmark of PD.[51]

Although limited to a sample size too small to be statistically significant, the apparent successes reported by Luong, et al. and Costantini, et al. on the use of high-dose parenteral thiamine therapy in the treatment of patients with PD is suggestive that thiamine therapy may, in part, ameliorate pathological changes associated with PD.[2,30] Also limited to a small number of patients, in work that further suggests an association between PD treatment and thiamine, Jimenez-Jimenez, et al. found that patients undergoing levodopa therapy had significantly higher CSF TDP and total thiamine levels than those not treated with this drug, suggesting the possibility of an additional mechanism, other than dopamine replacement, for the therapeutic benefits attained by levodopa in PD.[46]

Pan, et al. postulated that benfotiamine may be responsible for cognitive improvement in AD by improving brain energy.[52] This might also be the mechanism by which benfotiamine may improve brain function in PD and is consistent with the findings by Mizuno, et al. of low KGDHC in the SN in patients with PD.[41]

Costantini, et al. hypothesized that in the centers typically affected by PD, a dysfunction of thiamine-dependent metabolic processes could cause focal and severe TD, leading to neural damage and might be a fundamental molecular event provoking neurodegeneration.[29,30] Such dysfunction might be due to impaired active intracellular transport of thiamine or to structural enzymatic abnormalities involved in thiamine metabolism. The clinical manifestations of PD may result from this localized neuronal damage and abnormalities in thiamine-dependent processes in PD might be overcome by diffusion-mediated transport at supranormal thiamine concentrations. Such high thiamine concentrations could be achieved with either parenteral therapy, as was used by Costantini, et al. and Luong, et al., or by oral benfotiamine, as was administered in the case reports described in this paper. Although their work did not reach statistical significance, Pan, et al. and Gibson, et al. reported success using oral benfotiamine in improving cognition in people with AD. It is tempting to speculate that there may be, in an analogous fashion as speculated by Costantini, et al. in the case of PD, a focal defect in thiamine metabolism in those centers that dysfunction in AD and that high levels of thiamine attained from benfotiamine therapy may improve function in these affected neurons.

Impaired thiamine utilization, whether due to its deficiency, defective metabolism, or transport, induces neurodegeneration. Thiamine therapy has been shown to often be protective in these instances. Oral benfotiamine has been shown to raise thiamine to the levels attained with parenteral thiamine. The decrease in symptoms in the cases reported here is consistent with the improvement reported in patients with PD following high-dose parenteral thiamine therapy by two separate research groups. It suggests, as posited by Costantini, et al., that supranormal thiamine levels could have a positive effect on the symptoms of PD. Beneficial effects from some other yet-to-be-determined action or actions of benfotiamine or methylcobalamin may also be a factor. These observations are also consistent with the findings reported by other researchers on the benefits obtained with the use of benfotiamine in the treatment of patients with AD and in one published case report in which improvement in the symptoms of ALS was noted following the use of benfotiamine and methylcobalamin. Costantini, et al. reported success with the use of high-dose parenteral thiamine in the treatment of several patients with various neurodegenerative diseases. Conclusions from these observations should be taken with caution as the cohorts treated were too small to reach statistical significance. However, if the benefits of high-dose thiamine–either by the injection of thiamine or by the use of oral thiamine, benfotiamine, or another thiamine derivative–in the treatment of these and other neurodegenerative diseases is verified by future studies, it would support the hypothesis of a common mechanism in which certain neurodegenerative diseases are, at least in part, a consequence of defects in thiamine processing in focal areas of the brain and the symptoms expressed in these diseases are the result of impaired thiamine utilization in those discrete areas of the brain. A large multicenter study on treating AD with benfotiamine is currently underway. Considering the high safety profile of benfotiamine and the suffering caused by neurodegenerative diseases, appropriate studies, with sufficiently large cohorts to reach statistical significance, on the effects of benfotiamine on PD, ALS, FTD, and other neurodegenerative diseases are urgently needed.

Conclusions

Patients with PD have been shown to have lower levels of vitamin B12 than controls. Higher levels of serum vitamin B12 at the time of diagnosis of PD appear to correlate with a lower risk of future dementia. Thiamine deficiency is a well-established cause of

neurodegeneration, and its impaired utilization in the dopaminergic neurons of the SN may be a possible factor in PD. The improvement in the symptoms of patients with PD noted following the administration of parenteral high-dose thiamine therapy, the case reports described in this paper, as well as other findings on the benefits of thiamine therapy in the treatment of PD, strongly suggest the need for further research on the potential beneficial effects of benfotiamine as well as combination therapy of benfotiamine and methylcobalamin in the treatment of PD.

Author Details

Dr. Mann is an independent researcher on the use of nutrients to improve patients' central and peripheral neurological function. He is a key opinion leader and has given lectures at over a hundred domestic and international medical conferences. In June 2023, he published a scientific peer-reviewed article entitled "Impaired Thiamine Metabolism in Amyotrophic Lateral Sclerosis and Its Potential Treatment with Benfotiamine: A Case Report and a Review of the Literature" (10.7759/cureus.40511).

Dr. Baratta is a renowned authority on neurodegenerative diseases and authored, "A Compendium of Degenerative Brain Diseases" in 2001 which is used in medical schools globally. In June of 2023, he was the managing editor of "The Misdiagnosis Casebook in Clinical Medicine" published by Springer Nature. He is a former medical school dean, chairman and professor of the department of integrated clinical medicine. Dr. Baratta is a key opinion leader, speaker, published author, and editor of several medical textbooks by Springer Nature. As a mentor, he assists medical students who strive to publish medical articles in various scientific journals and as chapter authors of medical textbooks.

Disclosures

Disclosures

Dr. Richard H. Mann holds a financial interest in Zobria Labs, LLC and Realm Labs, LLC, companies that distribute nutritional supplements, including benfotiamine and methylcobalamin. Dr. Mann serves as the Chief Scientific Officer at Zobria Labs, LLC and Realm Labs, LLC. Dr. Larry G. Baratta has no relevant financial relationships or disclosures to report.

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