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VITAMIN B_6 (PYRIDOXINE) THERAPY FOR CARPAL TUNNEL SYNDROME

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Ellis and coworkers[12] were the first to describe the coexistence of vitamin B_6 deficiency and a syndrome including carpal tunnel syndrome (CTS) in 1976.[12] Subsequently, they reported resolution of CTS symptoms with vitamin B_6 administration, and concluded that CTS was caused by a deficiency of that vitamin.[13, 18] Ellis and coworkers have continued to publish numerous papers supporting this hypothesis,[10, 11, 14–17, 20, 21, 33] while other authors demonstrated a lesser association and effect of vitamin B_6 in CTS.[22, 23] Other papers, however, have not shown a correlation between vitamin B_6 deficiency and CTS and contest the role of vitamin B_6 in CTS therapy.[1, 4, 6–8, 29, 31, 35, 36] This article reviews the actions of vitamin B_6 and the literature debating the role of vitamin B_6 in CTS therapy. Some papers have questioned the accuracy of the diagnoses of vitamin deficiency and carpal tunnel syndrome in these patients.

HISTORY

György[5] is credited with observing the appearance of dermatitis in rats fed a vitamin B complex-deficient diet supplemented with thiamine and riboflavin in 1933. He named the missing nutrient vitamin B_6. This water-soluble vitamin (pyridoxal) first was isolated in crystalline form by Lepovsky in 1938 and synthesized by Harris and Folkers in 1939. Snell[5] described the various forms of pyridoxine found in vivo between 1944 and 1948. These consist of six compounds—pyridoxine (PN), pyridoxal (PL), and pyridoxamine (PM) (respectively the alcohol, aldehyde, and amine substitutions at the 4′ position) and their 5′ phosphated esters (designated PNP, PLP, and PMP; e.g., pyridoxal phosphate = PLP).[27]

VITAMIN B_6 ACTIONS AND DEFICIENCY

The actions of vitamin B_6 are numerous. PLP functions as a coenzyme in amino acid metabolism and links carbohydrate, amino acid, and fat metabolism. Biogenic amines, such as dopamine, serotonin, histamine, and γ-amino butyric acid (GABA) are synthesized or metabolized through PLP-dependent enzyme reactions. Vitamin B_6 also is essential to the development of brain lipids and myelination of nerve fibers in the central nervous system. Vitamin B_6 therefore is involved in the structural and functional integrity of the nervous system.[27]

Vitamin B_6 also is critical in the metabolism of folic acid and vitamin B_{12}. PLP is a major active form of vitamin B_6 and has been named as a cofactor in over 100 biochemical reactions. PLP and PL account for 75% to 80% of circulating vitamin B_6.[27]

Vitamin B_6 deficiency can be seen in various forms. In infants, findings include abnormal electroencephalographic (EEG) tracings, convulsions, decreased GABA, altered amino acid levels, and decreased fatty acid levels in the brain.[27, 28] In adults, signs and symptoms include dermatitis,

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neuritis, stomatitis, cheilosis, glossitis, irritability, depression, and confusion.[27]

Because pyridoxine is a central cofactor in the production of neurotransmitters, it has been a therapeutic adjunct in conditions such as Parkinson's disease, depression, chronic pain, behavioral abnormalities, and peripheral neuropathy.[6, 28] It is well known that vitamin B_6 deficiency can cause a peripheral neuropathy, which reverses with vitamin B_6 administration.[5, 27, 28] Interestingly, overconsumption of vitamin B_6 can lead to motor and sensory neuropathy.[6, 37]

VITAMIN B_6 LEVELS

Vitamin B_6 levels can be measured by direct and indirect assays. Direct assays of vitamin B_6 measure plasma PLP and PL concentrations. PL is the form of B_6 that crosses into the cell, so PL levels indicate the bioavailability of vitamin B_6.[27]

Indirect assays include urinary metabolites of the tryptophan and methionine pathways, as well as PLP-dependent enzyme activities (such as erythrocyte glutamic-oxaloacetic transaminase [EGOT].) These tests therefore measure vitamin B_6 utilization and metabolism. There currently is a limited understanding of the temporal relationship between pyridoxine ingestion and changes in enzyme activities however.[27]

LITERATURE SUPPORTING THE ASSOCIATION OF CARPAL TUNNEL SYNDROME AND VITAMIN B_6 DEFICIENCY

Of the many papers in support of an association between CTS and B_6 deficiency, most were authored by Ellis, Folkers, and their associates.[10–21, 33] Ellis and coworkers[13, 18] presented data on 10 patients with vitamin B_6 deficiency by EGOT assay and having CTS by history and clinical examination. The symptoms used by Ellis and coworkers[13, 18] to diagnose CTS included numbness and tingling of the hands, edema of the feet and ankles, nocturnal paralysis, muscle spasm of the extremities, paraesthesias of the face, and painful shoulders and knees. Vitamin B_6 levels were brought to normal levels in 2 to 4 weeks of pyridoxine therapy and the patients' hand and other symptoms resolved.

Ellis and coworkers presented another group of 11 patients diagnosed with CTS by the same diffuse clinical symptoms in 1977.[12] Each was tested with the EGOT assay for PLP activity and found to be deficient. Electromyographs (EMGs) were done on all 11 patients at the outset of the study and on 10 patients after 6 weeks of vitamin B_6 therapy. Only four of the pretreatment EMGs are commented on in the paper; only one was diagnostic. The EMG data from 6 weeks reportedly showed no change. The authors stated that CTS may be present with no evidence of EMG abnormalities. Of the seven people treated, all responded symptomatically.

In two following papers, Folkers, Ellis and coworkers[17, 20] presented the results of a single patient. They believed his response demonstrated the causal relationship of vitamin B_6 deficiency and CTS. The patient was treated with various doses of pyridoxine for 11-week intervals. The patient's generalized clinical symptoms resolved and returned, corresponding to pyridoxine dosage. EMG analysis of this patient pre- and posttreatment showed little change, with conduction through the carpal tunnel still prolonged. These papers document only one patient's clinical trial. Despite the authors' enthusiasm that pyridoxine is curative of CTS, this case study does not seem to prove their statement. It remains in question whether this patient had CTS or peripheral neuropathy truly caused by vitamin B_6 deficiency.

In a study similar to those just described, Ellis et al[14] studied seven patients in a double-blind randomized study (four treatment, three control). They noted that higher EGOT assay values correlated with decreasing symptoms. They concluded that a low specific activity for the EGOT assay was diagnostic of the severity of B_6 deficiency and the severity of CTS. They also attributed failure in treatment of several patients to failure of compliance because of lack of change in EGOT assay values.

Ellis and Folkers[10, 15] also published several reviews of the history of their work, either individually or together. Despite their strong conclusions, the evidence supporting their thesis is largely anecdotal and subjective.

Because these authors claim clinical success treating a broad group of conditions including CTS, de Quervain's tenosynovitis, diabetic neuropathy, and shoulder–hand syndrome with pyridoxine,[10] it is conceivable that there is some effect of vitamin B_6 on painful conditions other than at the site of pathology. (Pain modulation and vitamin B_6 will be reviewed in a later section.) The underlying reason for the effectiveness of vitamin B_6 in patients with painful conditions or a peripheral neuropathy may be an indirect action of B_6 on pain perception, and not by reversal of the neuropathy.[7]

Other authors have reported some success with vitamin B_6 therapy. Kasdan and Janes[23] reported that vitamin B_6 therapy alone or B_6 with wrist splints or job change for CTS showed 68% full or satisfactory alleviation of symptoms. This was a large increase over a previous group, in which conservative therapy (combinations of wrist splints, job changes, anti-inflammatory agents, and steroid injections) showed only a 14% success rate. Because of the retrospective nature of this study, it was impossible to assign a direct relationship between the cessation of symptoms and vitamin B_6 administration in this set of patients. The outcome of those treated with pyridoxine appeared significantly better, however.

LITERATURE REFUTING THE VALUE OF B_6 IN CARPAL TUNNEL SYNDROME

In an attempt to decipher the role of peripheral neuropathy and vitamin B_6 levels, Byers and coworkers[8] studied 33 patients divided into four groups using nerve conduction and EMG data: (1) CTS only, (2) peripheral neuropathy, (3) CTS and peripheral neuropathy, and (4) normal patients. They demonstrated that EGOT activity did not differ between normal patients and those with CTS only. When comparing vitamin B_6 levels of patients with and without peripheral neuropathy regardless of CTS, however, there was a highly significant correlation. There was no difference in pyridoxine metabolic activity when the groups were separated on the basis of CTS. Patients with CTS responsive to pyridoxine therefore may have an unrecognized peripheral neuropathy of which CTS is a manifestation. This work correlates with that of Smith et al,[34] who found no pyridoxine deficiencies in their patients with CTS.

Amadio[1] reported a series of 19 patients with CTS treated conservatively. Of four patients with six mildly involved hands (median nerve paresthesia and pain), four hands improved with vitamin B_6 therapy. Of patients with moderate symptoms, none improved with vitamin B_6 supplementation. When the vitamin B_6 therapy was combined with splinting and steroid injections, approximately one-third had symptomatic relief. Two thirds of patients with median neuropathy required surgical release after 3 months of conservative therapy. This study concluded that vitamin B_6 may be an adjunct to conservative treatment of CTS, but the effectiveness of vitamin B_6 was seen in a minority of cases.

Monsivais and coworkers[29] studied 35 manual laborers with 67 hands diagnosed with CTS who declined surgical release. Treatment modalities involved splinting, steroid injection, vitamin B_6 administration, and nonsteroidal anti-inflammatory medications. Of 35 patients, one improved, three worsened and the rest remained unchanged. Conservative treatment, including vitamin B_6, was of little value in these manual workers. The duration and dosage of pyridoxine was poorly documented, but, because so few patients improved, it is improbable that these patients' symptoms were caused purely by a vitamin deficiency that would have been resolved with vitamin administration.

In a randomized double-blind study by Stransky and coworkers,[36] 15 patients were divided into control, vitamin B_6-treated, and placebo groups. The patients were diagnosed with CTS by electrodiagnostic studies. Of the four control patients, three improved over the 10 weeks and one worsened. Four of five in the placebo group also improved; the fifth worsened. Three of four pyridoxine-treated patients improved; three were unchanged. No significant changes were seen in nerve conduction or EMGs following therapy. Based on these results, no advantage of PN was seen over other forms of conservative therapy. EMGs were found not to parallel the clinical symptoms or course.

Spooner and coworkers[35] reported on a series of 35 patients who had criteria for idiopathic CTS based on clinical diagnosis and electrophysiologic data (two separate clinical examinations with at least one provocative sign and abnormal median palmar distal latency.) The patients were randomized into treatment or control groups. The treatment group received 200 mg of pyridoxine daily and the control, a placebo. Amino transferase (a PLP-dependent enzyme) activity was measured pretreatment and at 6 and 12 weeks to assess compliance with pyridoxine therapy. The treatment group showed a statistically significant reduction in symptoms of swollen fingers and tingling after repetitive motion. No significant differences were seen between treatment and control patients, however, with respect to nocturnal pain, numbness, and tingling at rest nor was there a change in provocative signs or EMG data after treatment. This study was one of the largest randomized, well-controlled trials of the use of pyridoxine in CTS to date.

Scheyer et al[32] reported pyridoxine had no effect on nerve conduction across the carpal canal, as well as pain and paraesthesias in the median nerve distribution, despite 400 mg/day administration of B_6 for 6 weeks followed by 100 mg/day thereafter in patients with CTS. They concluded that the absence of changes in EMG data indicated that pyridoxine was not effective in the treatment of CTS.

Another area of debate surrounds the accurate diagnosis of pyridoxine deficiency. The enzyme test used in the majority of the papers supporting vitamin B_6 therapy was described by Kishi.[26] It measures EGOT activity in erythrocytes.[26] Questions have been raised regarding the true normal range of enzyme activity. Azuma and coworkers[4] found over 50% of asymptomatic persons to be vitamin B_6-deficient using the criteria of Kishi.

Fuhr and coworkers[22] showed a large amount of overlap in EGOT assay results between control and CTS patients. Some patients with CTS did have a B_6 deficiency; others did not. Smith and coworkers[34] found no abnormalities in pyridoxal or pyridoxal phosphate in plasma neutrophils or red cells in a series of six patients with CTS.

DOSAGE AND COMPLICATIONS OF VITAMIN B_6 ADMINISTRATION

The recommended daily allowance of vitamin B_6 has been measured between 1.4 and 2.1 mg. This varies depending upon pregnancy status of the individual.[28] Other references[19, 27] recommend 2 to 4 mg/day.

Development of sensory and motor neuropathy secondary to excessive pyridoxine ingestion has been described.[19, 28, 30, 31] In one series, 13 of 16

patients were ingesting over 2 g/day of vitamin B_6 and one of the patients had taken vitamin B_6 at a level of 200 mg/day for 3 years when symptoms developed.[31] The amount needed before toxicity is unclear. A high quantity is needed before developing peripheral neuropathy, paresthesia, ataxia, weakness, and other neurologic complications.[19, 30, 31] Pyridoxine supplementation, if necessary, should be ingested at a rate of 200 mg/day or less and decreased after B6 levels have normalized.

THEORIES OF B_6 EFFECT ON PAIN

Effects on pain reduction with pyridoxine have been shown in clinical and laboratory studies.[7] Two possible mechanisms have been postulated for an antinociceptive property of pyridoxine. The first is that pyridoxine could inhibit presynaptic release of neurotransmitters from afferent pain fibers and the second is that it enhances the synthesis of serotonin and GABA, which contribute to the inhibition of pain-related information in the spinal cord and brain.[35] This information may explain why patients responsive to pyridoxine therapy have unchanged electrodiagnostic tests. The neural dysfunction is still present despite symptomatic improvement. A change in pain perception or pain threshold could create this clinical picture. Some authors[35] caution that patients who report less discomfort actually may have progressive nerve damage and functional deterioration.

DISCUSSION

The body of literature involving pyridoxine administration to patients with CTS has many conflicting reports and conclusions. The body of literature of Ellis, Folkers and coworkers supports the theory that CTS is caused by vitamin B_6 deficiency. Their studies are difficult to evaluate for several reasons, including the probability of confounding diagnoses, small sample size, and methodologic problems in establishing vitamin deficiency. The description of their patients' findings that (they called CTS) clearly included symptoms not related to median neuropathy at the wrist. In addition, symptoms of generalized peripheral neuropathy were among their criteria. The possibility that these patients had median neuropathy as part of a generalized neuropathy has been suggested by other reviews[1, 9] and is consistent with other studies.[8, 34] The correct diagnosis of these patients is further obscured by the lack of electrodiagnostic studies and incomplete reporting of data.[12, 13, 18] Nerve conduction studies generally are regarded as the gold standard in CTS diagnosis, with a sensitivity of over 80%.[24] Symptoms such as nocturnal pain and paraesthesias, as used by these authors, have been shown to be poorly specific.[25] Provocative testing such as Tinel's and Phalen's signs have been shown to have sensitivities of 25% to 75% and specificity of 47% to 90%.[24] Another criticism of the vitamin B_6 deficiency hypothesis is that the patients of Ellis et al had none of the normal stigmata of B_6 deficiency (i.e., stomatitis, glossitis, dermatitis).

The literature refuting the value of vitamin B_6 in CTS contains studies with larger patient populations and well-defined criteria for diagnosis of CTS, including electrodiagnostic testing, screening out those patients who may have a peripheral neuropathy. It should be stressed that patients with CTS should be diagnosed carefully. Electrodiagnostic tests should document neuropathy at the carpal tunnel and rule out neuropathy at other sites, indicative of a more generalized neuropathic condition. No controlled randomized perspective study has shown vitamin B_6 to be clearly efficacious over other conservative treatments for CTS.

SUMMARY

The literature at this time does not give convincing evidence for use of pyridoxine as the sole treatment when confronted with a patient with idiopathic CTS. It may be of value as an adjunct in conservative therapy through altered perception of pain and increased pain threshold. For patients not responsive to conservative therapy, surgical decompression of the carpal canal is the treatment of choice.

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