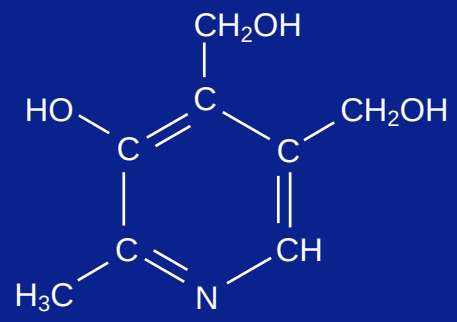
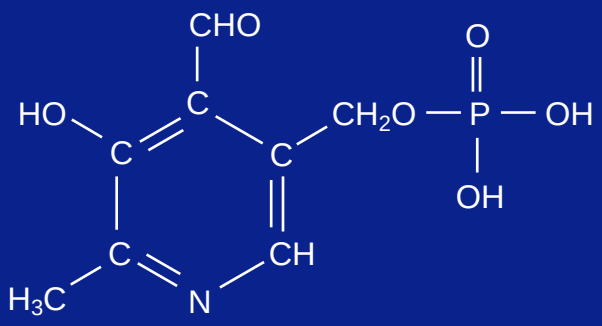
Pyridoxine



Pyridoxal 5' Phosphate



Monograph

Vitamin B6 (Pyridoxine; Pyridoxal 5'-Phosphate)

Introduction

Vitamin B6 consists of three related pyrimidine vitamer derivates: pyridoxine, pyridoxal, and pyridoxamine, and their phosphate esters. The metabolically active coenzyme form of vitamin B6 is pyridoxal 5'-phosphate (P5P).[1] B6 vitamers are first oxidized to pyridoxal, and rapidly phosphorylated to P5P in the liver.[2] P5P is the main circulating form exported from the liver and is considered the most relevant direct measure of vitamin B6 status.[3]

Pyridoxine was first isolated in 1934 and named by Albert Szent-Gyorgy.[1] The standard B6 vitamin supplement is pyridoxine hydrochloride (HCl), which is the least expensive to produce commercially;[4] however, P5P is the only form which can be used by the enzymes involved in biochemical processes, which are associated with nitrogen and protein metabolism and heme synthesis.[5] Plasma P5P levels were found to be significantly lower than normal in 22 out of 31 patients with impaired liver function, which reflects the liver's importance in B6 conversion. In patients receiving pyridoxine HCl, only 33 percent responded with an increase in plasma P5P, while all of the patients receiving P5P responded with an increase.[6]

Biochemistry/Pharmokinetics

Pyridoxine is water soluble and stable in heat and acid mediums, while it is unstable in alkaline solutions and light.[7] Pyridoxine and its vitamers are absorbed in the upper small intestine by simple diffusion and transported to the liver for biotransformation into the active coenzyme P5P, which is then exported from the liver bound to albumin. Uptake into tissue is by extracellular de-phosphorylation, followed by metabolic trapping intracellularly as P5P.[8]

P5P-dependent enzymes are involved in the following reactions:[8]

- decarboxylation of amino acids to yield amines, many of which are important neurotransmitters and hormones.
- transamination of amino acids to keto-acids, which are then oxidized and used as metabolic fuel.
- phosphorolytic cleavage of glycogen (from liver and muscle) to glucose-one-phosphate.
- formation of alpha aminolevulinic acid, a precursor to heme.
- decarboxylation of phosphatidylserine to phosphatidylethanolamine in phospholipid synthesis.
- as a co-factor in a variety of reactions involving side-chain cleavage, including cystathionine synthase and cystathionase.

Clinical Applications

Anemia

P5P is necessary for the activation of glycine in the initial stages of heme production. Several cases of B6-responsive anemias have shown no response to pyridoxine and prompt response to P5P. This suggests an enzymatic deficiency or inhibition of pyridoxal kinase.[9] In another study, excessive alcohol produced bone marrow sideroblastic changes that were responsive to P5P, while no response was achieved from pyridoxine or folic acid.[10] From a therapeutic point of view, P5P should be tried in all cases of symptomatic primary sideroblastic anemia which have shown no response to pyridoxine.[9]

In 16 patients with sickle cell anemia, plasma P5P concentrations were significantly lower than in 16 controls. Oral supplementation of five of the patients with 50 mg pyridoxine twice daily for two months resulted in increased plasma P5P levels.[11] Since pyridoxine and P5P have been shown to have anti-sickling properties *in vitro*,[12,13] these studies suggest P5P supplementation may also be of therapeutic benefit *in vivo* in sickle cell anemia.[11]

Carpal Tunnel Syndrome

Researchers have found a direct correlation between carpal tunnel syndrome (CTS) and a deficiency in P5P, and that treatment with 100-200 mg pyridoxine daily for at least 12 weeks was highly beneficial in reducing both the symptomology and a P5P deficiency associated with CTS.[14-16] A few studies have shown no clinical benefit from pyridoxine HCl supplementation,[17-19] with most of the reports of beneficial effects coming from Ellis et al.[15,20-23] A 1996 literature review of clinical trials using pyridoxine to treat CTS concluded that the evidence for the use of pyridoxine as the sole treatment for CTS is weak, but that it may be valuable as an adjunctive treatment through its effect on altered perception of pain and increased pain threshold.[24]

Premenstrual Syndrome (PMS)

B6 nutritional status has a significant and selective modulatory impact on central production of both serotonin and GABA – neurotransmitters that control depression, pain perception, and anxiety.[25] P5P is a cofactor in the synthesis of these neurotransmitters.[26] Authors of a 1999 review of published and unpublished randomized placebo-controlled trials of the effectiveness of vitamin B-6 in the management of PMS concluded that the pooled data of nine trials representing 940 patients suggests doses of pyridoxine up to 100 mg/day are likely to be of benefit in treating premenstrual symptoms, including premenstrual depression.[27]

Hyperhomocysteinemia

High levels of plasma homocysteine are considered an independent risk factor for atherosclerotic disease and venous thrombosis. Homocysteine, an intermediate in methionine metabolism, can be re-methylated to methionine, or be channeled down the trans-sulfuration pathway to cysteine, which requires two P5P-dependent enzymes: cystathionine synthase and cystathionase.[8]

A study of 1,160 elderly subjects (67-96 years) correlated high homocysteine levels with low folate and B6.[28] Results of the 1998 Nurses' Health Study showed cardiovascular disease risk was lowest among those women with the highest intakes of folate and B6.[29] Vitamin therapy – a combination of folic acid (500 mcg) and pyridoxine (100 mg) – in 49 hyperhomocysteinemic persons, significantly reduced fasting plasma homocysteine concentrations (median 13.9 to 9.3 mM/L, reduction 32%) and post-methionine load concentrations (median 55.2 to 36.5 mM/L, reduction 30%).[30]

Studies that have tried to distinguish between the potential beneficial effects of folate vs B6 have shown folate to be more efficacious in lowering serum homocysteine. One study showed that, while folic acid 650 mcg/day lowered fasting homocysteine in moderately hyperhomocysteinemic subjects, 10 mg B6/day had no effect.[31] A similar study showed folic acid 400 mcg/day reduced plasma homocysteine in people with non-elevated homocysteine levels while pyridoxine 2 mg/day had no effect.[32] It should be noted, however, that 10 mg/day and 2 mg/day B6 are quite low doses.

Other Clinical Indications

A double-blind trial using pyridoxine (25 mg every eight hours for three days) in the treatment of morning sickness resulted in a significant reduction in vomiting, and an improvement in nausea in those who initially reported severe nausea.[33]

Researchers in Japan published animal studies suggesting that B6 deficiencies impair conversion of alpha-linolenic acid to EPA and DHA, with the most pronounced reduction in production of DHA.[34]

P5P has also been shown to protect rat kidneys from the nephrotoxicity of aminoglycoside antibiotics.[35] Pyridoxine in low doses (10 mg/day) is also of therapeutic value for hyperoxaluric kidney stone formers.[36]

Animal studies have shown that B6 depletion leads to the development of hypertension, which is normalized within 24 hours by repletion with the vitamin.[37] There are several proposed mechanisms for this effect, but none that are proven.

There are many more proposed indications for P5P such as asthma, autism, acne, diabetes mellitus, depression, toxemia of pregnancy, and side effects of oral contraceptives, which are less clinically and experimentally documented.[38-44]

Safety, Toxicity, and Side Effects

The use of supplemental P5P has not been associated with toxicity, although the inactive form, pyridoxine, has been associated with reports of peripheral neuropathy.[45] One hypothesis is that pyridoxine toxicity is caused by exceeding the liver's ability to phosphorylate pyridoxine to P5P, yielding high serum levels of pyridoxine which may be directly neurotoxic or may compete with P5P for binding sites, resulting in a relative deficiency.[46]

Mpofu et al reported electrophysiological and neurological examination of 17 homocystinuric patients who had been treated with 200-500 mg pyridoxine HCl daily for 10-24 years, and found no evidence of neuropathy.[47] Most reported cases of neuropathy associated with pyridoxine supplementation have involved intake of at least 500mg/day for two years or more.[48] While there is no doubt that

vitamin B6 can be neurotoxic in gross excess, there is considerable controversy over the way in which toxicological data have been translated into advised limits.[8]

Drug/Nutrient Interactions

The antituberculosis drug isoniazid can result in a functional vitamin B6 deficiency.[49]

Anti-parkinsonian drugs benserazide and carbidopa cause vitamin B6 depletion by forming hydrazones.[50]

Pyridoxine will reduce the efficacy of levodopa in controlling parkinsonian symptoms, the magnitude of the effect proportional to the dose of pyridoxine.[51]

There have been many reports of abnormal tryptophan metabolism in women taking either oral contraceptive or menopausal hormone replacement therapy, which have been interpreted as indicating estrogen-induced vitamin B6 deficiency or depletion.[8]

Dosage

While the RDA for adults is 2-4 mg daily, the typical therapeutic dose is 50-200 mg/day.

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