supplement and food labels, is 5,000 IU (International Units). The basis for the DV for vitamin A is the U.S. RDA.

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Vitamin B_6

DESCRIPTION

Vitamin B_6 is the collective term for a group of three related compounds, pyridoxine (PN), pyridoxal (PL) and pyridoxamine (PM), and their phosphorylated derivatives, pyridoxine 5'-phosphate (PNP), pyridoxal 5'-phosphate (PLP) and pyridoxamine 5'-phosphate (PMP). Although all six of these vitamers should technically be referred to as vitamin B_6, the term vitamin B_6 is commonly used interchangeably with just one of the vitamers, pyridoxine. Vitamin B_6, principally in

the form of the coenzyme pyridoxal 5'-phosphate, is involved in a wide range of biochemical reactions, including the metabolism of amino acids and glycogen, the synthesis of nucleic acids, hemoglobin, sphingomyelin and other sphingolipids, and the synthesis of the neurotransmitters serotonin, dopamine, norepinephrine and gamma-aminobutyric acid (GABA).

Food sources of vitamin B_6, include meat, poultry, fish, eggs, white potatoes and other starchy vegetables, noncitrus fruits, fortified ready-to-eat cereals and fortified soy-based meat substitutes. The principal forms of vitamin B_6 in animal products are pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate. In plant-derived foods, the major forms of vitamin B_6 are pyridoxine, pyridoxine 5'-phosphate and pyridoxine glucosides. Glycosylated forms of pyridoxine range from approximately 5% to 75% of the total vitamin B_6 content in fruits, vegetables and grains, with little to none in animal products. Pyridoxine appears to be the only glycosylated form of vitamin B_6. The major glycosylated form of pyridoxine in most plant-derived foods is pyridoxine 5'-beta-D-glucoside. Pyridoxine hydrochloride is the form of vitamin B_6 most commonly used for fortification of foods and in nutritional supplements.

The classical symptoms and signs of vitamin B_6 deficiency are a microcytic, hypochromic anemia, seizure activity, seborrheic dermatitis, confusion and depression. Vitamin B_6-deficiency states in infants and children primarily result in electroencephalogram abnormalities and seizure activity, while in adults, vitamin B_6 deficiency primarily results in cheilosis (chapping and fissuring of the lips), glossitis (inflammation of the tongue), stomatitis (inflammation of the oral mucosa), anemia, irritability, confusion and depression. Many of these signs are not specific for vitamin B_6 deficiency and may be due to deficiencies of other vitamins or result from other causes. Vitamin B_6 deficiency may result from the use of certain drugs, including isoniazid (isonicotinic acid hydrazide or INH), penicillamine, cycloserine, ethionamide, hydralazine and theophylline. Subclinical vitamin B_6 deficiency frequently occurs in those with malabsorption syndromes, uremia, cancer, heart failure and cirrhosis, and in alcoholics, the elderly and adolescent females and during pregnancy. In the elderly and in those with malabsorption syndromes, clinical deficiency of the vitamin may occur.

In addition to vitamin B_6 deficiency conditions, vitamin B_6-dependency conditions exist. Certain inborn errors of metabolism exist in which a vitamin B_6-dependent enzyme is defective in the coenzyme (pyridoxal 5'-phosphate) binding site, and the enzyme only has significant activity when the tissue concentration of pyridoxine 5'-phosphate, the biologically active form of vitamin B_6, is much higher than normal. These vitamin B_6-dependent conditions, which may be responsive to treatment with large doses of the vitamin, include convulsions of the newborn secondary to glutamate decarboxylase (GAD) deficiency, cystathionuria secondary to cystathionase deficiency, gyrate atrophy with ornithinuria secondary to ornithinine-delta-aminotransferase deficiency, homocystinuria secondary to cystathionine beta-synthase deficiency, primary hyperoxaluria type 1 secondary to peroxisomal alanine-glyoxylate transaminase deficiency, sideroblastic anemia secondary to delta-aminolevulinate synthase deficiency and xanthurenic aciduria secondary to kynureninase deficiency. These genetic disorders are all rare.

Vitamin B_6 in the form of pyridoxal 5'-phosphate is a coenzyme for over 100 enzymes. Most of these enzymes are involved in amino acid metabolism and include aminotransferases (transaminases), decarboxylases. Pyridoxal 5'-phosphate is sometimes referred to as codecarboxylase. The basic chemistry accounting for the broad range of reactions of B_6 is Schiff's base formation. Schiff's bases are reaction products of aldehyde and amino groups. In the resting state of the above enzymes, the aldehyde group of pyridoxal 5'-phosphate is covalently linked to the epsilon-amino group of a lysine residue at the active site of the enzyme. Upon binding of the amino acid substrate, the lysine is exchanged for the alpha-amino group of the substrate, forming a Schiff's base with the aldehyde group of pyridoxal 5'-phosphate. A quinonoid intermediate follows the formation of the Schiff's base, which in turn is followed by the formation of the reaction products. Schiff's base chemistry is the mechanism of almost all of the reactions in which pyridoxal 5'-phosphate participates. One exception is the glycogen phosphorylase reaction. Glycogen phosphorylase catalyzes the breakdown of the storage polysaccharide glycogen to yield glucose 1-phosphate. Much of the total pyridoxal 5'-phosphate in the body is found in muscle bound to glycogen phosphorylase. In glycogen phosphorylase, the phosphate group of pyridoxal 5'-phosphate, rather than its aldehyde group, participates in the catalytic role of the enzyme.

Vitamin B_6 is involved in several key biological processes. Pyridoxal 5'-phosphate is the coenzyme for delta-aminolevulinate synthase, the first step in the synthesis of porphyrins. Heme is derived from protoporphyrin IX. Heme is the iron-containing prosthetic group that is an essential component of such proteins as hemoglobin, myoglobin and the cytochromes. Homocysteine is an intermediate in methionine metabolism and may undergo one of two metabolic fates, remethylation to L-methionine or further metabolism, leading to the synthesis of L-cysteine. The pathway leading to the synthesis of cysteine is known as the transsulfuration pathway. This pathway has two pyridoxal 5'-phosphate-

dependent enzymes: cystathionine beta-synthase and cystathionase. The conversion of tryptophan to niacin also requires pyridoxal-5'-phosphate, this time as a cofactor for the pyridoxal 5'-phosphate-dependent enzyme kynureninase. And, via its role in transamination, pyridoxal 5'-phosphate is involved in the production of energy.

Decarboxylation of amino acids yields amines, including gamma-aminobutyrate, dopamine, norepinephrine, epinephrine and serotonin, which play important roles as neurotransmitters or hormones. The amino acid decarboxylases are also pyridoxal 5'-phosphate-dependent enzymes. Pyridoxal 5'-phosphate plays a role in the regulation of steroid hormone activity: Physiological levels of pyridoxal 5'-phosphate interact with glucocorticoid receptors to downregulate their activity. Pyridoxal 5'-phosphate has also been shown to negatively modulate steroid-dependent gene expression induced by progesterone, androgen and estrogen hormones. Finally, serine hydroxymethyltransferase is a pyridoxal 5'-phosphate-dependent enzyme that catalyzes the interconversion of serine and glycine, both of which are major sources of one-carbon units necessary for the *de novo* synthesis of purine nucleotides, including thymidylate. Purine nucleotides are precursors of DNA and RNA, and thymidylate is a precursor of DNA.

The vitamers comprising the vitamin B_6 family are pyridine derivatives. Specifically, they are derivatives of 3-hydroxy-5-hydroxymethyl-2-methyl pyridine. The vitamers differ by the nature of the chemical group occupying the 4 position of the parent compound. In the case of pyridoxine, the 4 position is occupied by an hydroxymethyl group. Pyridoxine is also known as 5-hydroxy-6-methyl-3, 4-pyridinedimethanol, 2-methyl-3-hydroxy-4,5-bis(hydroxymethyl)pyridine and pyridoxol. Its molecular formula is $C_8H_{11}NO_3$ and its molecular weight is 169.17 daltons. Pyridoxine hydrochloride is the principal form of vitamin B_6 used in nutritional supplements and for food fortification.

Pyridoxal is also known as 3-hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridinecarboxaldehyde and 2-methyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine. In the case of pyridoxal, the 4 position of the parent compound is occupied by a formyl group. The molecular formula of pyridoxal is $C_8H_9NO_3$ and its molecular weight is 167.16 daltons. Pyridoxamine has an aminomethyl group occupying the 4 position of the parent structure. Pyridoxamine is also known as 4-(aminomethyl)-5-hydroxy-6-methyl-3-pyridinemethanol and 2-methyl-3-hydroxy-4-aminomethyl-5-hydroxymethylpyridine. Its molecular formula is $C_8H_{12}N_2O_2$ and its molecular weight is 168.18.

ACTIONS AND PHARMACOLOGY

ACTIONS

Vitamin B_6 has antineurotoxic activity and may have activity in a number of inborn errors of metabolism, including pyridoxine-dependent seizures in infants, sideroblastic anemia, primary hyperoxaluria, homocystinuria and cystathioninuria. Vitamin B_6 has putative antiatherogenic, immunomodulatory, anticarcinogenic and mood-modulatory activities.

MECHANISM OF ACTION

Vitamin B_6 is used in the prophylaxis and treatment of vitamin B_6 deficiency and peripheral neuropathy in those receiving isoniazid (isonicotinic acid hydrazide, INH). The antituberculosis drug isoniazid reacts non-enzymatically with pyridoxal 5'-phosphate to form a metabolically inactive hydrazone. This can result in vitamin B_6 deficiency and peripheral neuropathy. It may also result in pellagra. The formation of niacin from tryptophan is catalyzed by, among other enzymes, kynureninase. Kynureninase is a vitamin B_6-dependent enzyme. Therefore, vitamin B_6 deficiency resulting from isoniazid, particularly in the context of marginal or clinical niacin deficiency, may lead to the niacin deficiency disorder pellagra. The peripheral neuropathy resulting from isoniazid does not appear to be due to vitamin B_6 deficiency, but to isoniazid itself. The antineurotoxic effect of vitamin B_6 in the case of isoniazid appears to be accounted for by the reaction of the vitamin with the drug, thus lowering its tissue level and its neurotoxicity.

High theophylline levels may cause seizures. It is thought that this is due to reaction of theophylline with pyridoxal 5'-phosphate, leading to lowered plasma levels of the vitamin. Pyridoxal 5'-phosphate is involved in the metabolism of gamma-aminobutyric acid (GABA). GABA is a major inhibitory neurotransmitter in the central nervous system. When the concentration of GABA in the brain decreases to below a threshold level, seizures and other neurological disorders may occur. The concentration of GABA in the brain is controlled by two pyridoxal 5'-phosphate-dependent enzymes, glutamate decarboxylase (GAD) and GABA transaminase (GABA-T). A decrease in the levels of GABA in the brain secondary to decreased levels of pyridoxal 5'-phosphate can lead to seizures. It has been found that the administration of vitamin B_6 to mice treated with theophylline reduced the number of seizures, and the vitamin administered to rabbits reversed electroencephalogram changes caused by high doses of theophylline.

Seven inborn errors of metabolism are known in which a vitamin B_6-dependent enzyme has a defect in the coenzyme (pyridoxal 5'-phosphate) binding site, and the enzyme only has significant activity when the tissue concentration of pyridoxine 5'-phosphate is much higher than normal. The

disorders and their enzyme defects are pyridoxine-dependent seizures in infants (glutamate decarboxylase deficiency resulting in decreased CNS levels of GABA), pyridoxine-responsive sideroblastic anemia (delta-aminolevulinate synthase deficiency resulting in decreased synthesis of hemoglobin), primary hyperoxaluria type 1 (peroxisomal alanine-glyoxylate transaminase deficiency), homocystinuria (cystathionine beta-synthase deficiency), cystathioninuria (gamma-cystathionase deficiency), xanthurenic aciduria (kynureninase deficiency) and gyrate atrophy of the choroid and retina (ornithine-delta-aminotransferase deficiency). These disorders may be responsive to high doses of vitamin B_6, which increase tissue levels of pyridoxal 5'-phosphate.

The putative antiatherogenic activity of vitamin B_6 may be accounted for by a few different mechanisms. Hyperhomocysteinemia is a risk factor for atherosclerosis, coronary heart disease and stroke. L-homocysteine is a sulfur amino acid that is an intermediate in the metabolism of L-methionine. It is either remethylated to L-methionine via methionine synthase, which requires 5-methyl-tetrahydrofolate as a methyl donor, and methylcobalamin (a biologically active form of vitamin B_{12}) as a cofactor for its enzymatic activity, or, via the transsulfuration pathway, is converted to L-cysteine. Two pyridoxal 5'-phosphate-dependent enzymes are involved in the conversion of homocysteine to L-cysteine: cystathionine beta-synthase and gamma-cystathionase. Cystathionine beta-synthase catalyzes the reaction of homocysteine and serine to produce cystathionine, and gamma-cystathionase hydrolyzes cystathionine to form L-cysteine and alpha-ketobutyrate. Under physiological conditions, there is a balance between homocysteine formation and degradation. Elevation of plasma total homocysteine is associated with increased cardiovascular risk and over the past two decades a number of large prospective studies have shown that hyperhomocysteinemia is predictive for an increased relative risk of coronary events, stroke, venous thromboembolism, cognitive impairment and death. Recently it was shown that feeding mice a diet deficient in the B-vitamins pyridoxal 5'-phosphate (vitamin B_6), folic acid and cyanocobalamin (vitamin B_{12}) caused hyperhomocysteinemia and vascular cognitive impairment. The hypothesis that hyperhomocysteinemia is a cardiovascular risk factor first arose from clinical and pathological observations in children and young adults with the rare disease hereditary homocysteinemia. (Mutations in cystathionine beta-synthase are the most common cause of hereditary hyperhomocysteinemia.) Those with this affliction, if untreated, develop severe hyperhomocysteinemia with plasma homocysteine levels greater than 100 micromoles per liter (normal levels are from 5 to 15 micromoles per liter), which can lead to thromboembolic events, vascular lesions and death. The treatment is high doses of vitamin B_6, vitamin B_{12}, folic acid and betaine, and restriction of dietary methionine. However, several intervention trials have failed to show any clinical benefit of homocysteine-lowering therapy with B-vitamins. Interestingly, most of these trials were performed in subjects with relatively mild homocysteinemia (plasma levels between 10 and 30 micromoles per liter). Explanations for these negative trials range from insufficient statistical power of the trials, which would exclude a small clinical benefit, to concluding that mild hyperhomocysteinemia is not a causative risk factor. Clearly, further studies are needed and warranted.

Vitamin B_6, in the form of pyridoxine hydrochloride, has been found to lower systolic and diastolic blood pressure in a small group of subjects with essential hypertension. Hypertension is another risk factor for atherosclerosis and coronary heart disease. The mechanism of action of the antihypertensive effect of vitamin B_6 is unknown. Another study showed pyridoxine hydrochloride to inhibit ADP- or epinephrine-induced platelet aggregation and to lower total cholesterol levels and increase HDL-cholesterol levels, again in a small group of subjects. The mechanisms of action of the possible platelet and lipid effects of vitamin B_6 are unknown. Vitamin B_6, in the form of pyridoxal 5'-phosphate, was found to protect vascular endothelial cells in culture from injury by activated platelets. Endothelial injury and dysfunction are critical initiating events in the pathogenesis of atherosclerosis. The mechanism of the possible endothelial-protective effect of vitamin B_6 is unclear. It is thought that vitamin B_6 plays a role in the maintenance of endothelial integrity. Vitamin B_6 has been shown to have singlet oxygen quenching activity *in vitro*. Single oxygen is a reactive oxygen species and oxidative stress is thought to play a major role in the pathogenesis of atherosclerosis. Finally, vitamin B_6 is involved in the metabolism of (n-3) polyunsaturated fatty acids from alpha-linoleic acid to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). This may play some role in the putative antiatherogenic activity of vitamin B_6.

Both animal and human studies have demonstrated that vitamin B_6 deficiency affects cellular and humoral responses of the immune system. Vitamin B_6 deficiency results in altered lymphocyte differentiation and maturation, reduced delayed-type hypersensitivity (DTH) responses, impaired antibody production, decreased lymphocyte proliferation and decreased interleukin (IL)-2 production, among other immunologic activities. Those at risk for vitamin B_6 deficiency and associated immunological dysfunction are the elderly, those with uremia and those with HIV (human immunodeficiency virus) disease. Repletion of vitamin B_6 in those with vitamin B_6 deficiency can correct immunological dysfunctions. Supplementation of the vitamin in those who are vitamin B_6 sufficient, has not to date shown immune-

enhancing or immunomodulatory effects. The mechanism through which vitamin B_6 deficiency alters immune responses is not well understood. Vitamin B_6 deficiency appears to impair nucleic acid synthesis. The impaired nucleic acid synthesis is associated with altered one-carbon metabolism, particularly the activity of serine hydroxymethyltransferase. Serine hydroxymethyltransferase is a pyridoxal 5'-phosphate-dependent enzyme which catalyzes the interconversion of serine and glycine, both of which are major sources of one-carbon units necessary for the synthesis of purine nucleotides and thymidylate. Impairment of purine nucleotide and thymidylate synthesis would impair the synthesis of nucleic acids. Serine hydroxymethyltransferase activity appears to be low in resting lymphocytes. Antigenic or mitogenic stimulation of immune cells triggers their proliferation. Serine hydroxymethyltransferase activity increases in immune cells under the influence of antigenic or mitogenic stimulation, thus supplying the increased demand for nucleic acid synthesis during an immune response. Since vitamin B_6 is involved in the synthesis of nucleic acids, via serine hydromethyltransferase, deficiency of the vitamin would result in decreased DNA replication, with consequent decreases in RNA and protein synthesis and immune cell proliferation.

Pyridoxal has been found to inhibit the growth of human malignant melanoma cells *in vitro*. It has also been found to inhibit the growth of melanoma cells injected into mice. There is one report of topical vitamin B_6 inducing lesion regression in two patients with melanoma. The mechanism of the putative anticarcinogenic activity of vitamin B_6 is unknown. A recent Scottish large case-control observational study reported a moderately strong inverse association between vitamin B_6 intake and incidence of colorectal cancer. The mechanism of action of this possible anticancer effect is unclear.

Vitamin B_6 may be useful in managing the depressive symptoms in some women with premenstrual dysphoric disorder (PMDD), also known as premenstrual syndrome (PMS). However, the evidence for this comes mainly from poor-quality trials. The mechanism of this putative effect may be accounted for, in part, by the participation of pyridoxal 5'-phosphate as a coenzyme in the synthesis of the neurotransmitters serotonin and dopamine. Modulation of steroid-dependent gene expression, by the vitamin, may also play some role in this putative effect.

PHARMACOKINETICS

The major forms of vitamin B_6 from animal products are pryridoxal 5'-phosphate and pyridoxamine 5'-phosphate. The major forms of vitamin B_6 from plant-derived foods are pyridoxine, pyridoxine 5'-phosphate and pyridoxine glucosides. Pyridoxine hydrochloride is the principal form of vitamin B_6 used for food fortification and in nutritional supplements. Pyridoxal 5'-phosphate is also available as a nutritional supplement.

The phosphorylated forms of vitamin B_6 undergo hydrolysis in the small intestine via alkaline phosphatase, and the nonphosphorylated forms of the vitamin are absorbed by a nonsaturable passive diffusion process, mainly in the jejunum. The efficacy of absorption of vitamin B_6 is high and even extremely high doses of vitamin B_6 are well absorbed. The pyridoxine glucosides are less efficiently absorbed than the other vitamin B_6 forms. The pyridoxine glucosides are deconjugated by a mucosal glucosidase. A fraction of the pyridoxine glucosides is absorbed intact and hydrolyzed in various tissues.

Some vitamin B_6 is converted to pyridoxal 5'-phosphate in the enterocytes where it is used in various metabolic reactions. Most of the absorbed vitamin B_6 is transported via the portal circulation to the liver. In the liver, pyridoxine, pyridoxal and pyridoxamine are metabolized to pyridoxine 5'-phosphate, pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate, by pyridoxal 5'-phosphate kinase. Pyridoxal 5'-phosphate is secreted by the liver and transported by the systemic circulation to the various tissues of the body. Pyridoxal 5'-phosphate is the primary form of vitamin B_6 in the circulation and is bound to serum albumin.

The major body pool of vitamin B_6 is in muscle, where most of the vitamin is present as pyridoxal 5'-phosphate bound to glycogen phosphorylase. The principal catabolite of vitamin B_6 is 4-pyridoxic acid which is the primary form of the vitamin excreted in the urine. 4-Pyridoxic acid, which is principally formed in the liver, accounts for approximately 50% of the vitamin B_6 compounds in the urine. At very high doses of vitamin B_6, which is mainly in the form of pyridoxine, much of the dose is excreted unchanged in the urine.

INDICATIONS AND USAGE

INDICATIONS

Vitamin B_6 is used for the treatment of vitamin B_6 deficiency and for the prophylaxis of isoniazid-induced peripheral neuropathy. It may also be helpful in treatment of convulsions of the newborn secondary to glutamate decarboxylase deficiency, sideroblastic anemia secondary to delta-aminolevulinate synthase deficiency, primary hyperoxaluria type 1 secondary to peroxisomal alanine-glyoxylate transaminase deficiency, homocystinuria secondary to cystathionine beta-synthase deficiency, cystathioninuria secondary to gamma-cystathionase deficiency, xanthurenic aciduria secondary to kynureninase deficiency and gyrate atrophy of choroid and retina secondary to ornithinine-delta-aminotransferase deficiency.

Vitamin B_6 may be helpful in some women with premenstrual dysphoric disorder (PMDD), also known as premenstrual syndrome (PMS), and may be useful in some cases of gestational diabetes and for protection against metabolic imbalances associated with the use of some oral contraceptives. Results are mixed and largely negative with the respect to claims that vitamin B_6 is an effective treatment of carpal tunnel syndrome. There is very preliminary evidence that vitamin B_6 may help protect against atherosclerosis, that it might show some activity against melanoma and that it might be helpful in some neurologic conditions. It has some immune stimulating properties. It is an anti-emetic in some circumstances. There is little evidence to support claims that vitamin B_6 is an effective treatment for depression (other than, possibly, the depression associated with premenstrual syndrome), autism, schizophrenia, atopic dermatitis, alcoholism, diabetic peripheral neuropathy, Down's syndrome, dental caries, Huntington's chorea or steroid-dependent asthma.

RESEARCH SUMMARY

A recent review of randomized, double-blind, placebo-controlled trials of vitamin B_6 in the treatment of premenstrual syndrome (PMS) concluded that the treatment appeared to relieve overall premenstrual and premenstrual-associated depressive symptoms. Doses ranged between 50 milligrams and 600 milligrams of vitamin B_6 daily. Only one of 940 subjects included in these studies reported symptoms suggestive of sensory neuropathy, the principal adverse reaction of high dose vitamin B_6. Premenstrual symptoms appeared to be relieved by 100 milligrams of vitamin B_6 daily (typically in divided 50 milligram doses). There was less evidence of efficacy at a 50 milligram daily dose. Though the review authors found methodological flaws in many of the studies, several of which were of poor quality, they have stated that the available evidence warrants a large-scale multicenter clinical trial. Vitamin B_6's apparent efficacy in PMS has been speculatively attributed, in part, to its role as a cofactor in the synthesis of serotonin and dopamine, deficits in the availability and function of which may play a part in the pathogenesis of PMS.

There are reports that vitamin B_6 supplementation can help normalize disturbances in the metabolism of tryptophan associated with the use of some oral contraceptives. Studies suggest that 5 to 50 milligrams daily are adequate for this purpose. Improved glucose tolerance has been reported in some of these studies. Some other studies, however, have shown no vitamin B_6 effect on the nausea, vomiting, dizziness and irritability sometimes associated with the use of oral contraceptives. Evidence is conflicting and inconclusive with respect to vitamin B_6's impact on depression linked to the use of oral contraceptives.

Claims that vitamin B_6 is useful in improving glucose tolerance in diabetics in general is poorly supported except in gestational diabetes where the evidence is somewhat better, though still far from conclusive. More research is needed.

Studies on the use of vitamin B_6 in the treatment of carpal tunnel syndrome have produced mixed results which, on balance, suggest little benefit. Some open trials have found that vitamin B_6 is helpful, but most double-blind, placebo-controlled trials have reported no benefit. Until larger, better-designed studies are conducted, no useful conclusion can be reached with respect to vitamin B_6's role, if any, in treating carpal tunnel syndrome.

A lingering question is whether or not vitamin B_6 possesses antiatherogenic activity. Hyperhomocysteinemia is a risk factor for atherosclerosis, coronary heart disease and stroke. Results have been mixed on the ability of supplemental vitamin B_6 per se to lower homocysteine levels. Vitamin B_6, along with vitamin B_{12} and folic acid, lowers homocysteine levels in those with severe hyperhomocysteinemia, such as is found in the rare genetic disorder hereditary homocysteinemia, thus decreasing the risk of atherosclerosis, coronary heart disease, stroke and death in those individuals. Vitamin B_6 lowers homocysteine levels in pyridoxine-responsive homocystinuria and in patients with severe vitamin B_6 deficiencies. However, several intervention trials have failed to show any clinical benefit for homocysteine-lowering therapy with B-vitamins, including vitamin B_6, in subjects with relatively mild homocysteinemia. There is one uncontrolled report associating supplemental vitamin B_6 use with reduced incidence of acute cardiac chest pain and myocardial infarction. And there is a study showing a significant protective effect of vitamin B_6 on function and integrity of vascular endothelium subjected to experimental injury by activated platelets. There are also preliminary reports that supplemental vitamin B_6 can reduce hypertension in some. This work needs confirmation. A recent report of a large prospective study of middle-aged Japanese found a significant inverse association between vitamin B_6 intake and the risk of coronary heart disease, primarily myocardial infarction (MI). An approximately 40 to 50% reduction was found among individuals who consumed the highest quintile of dietary vitamin B_6 (median intake of 1.6 mg daily) compared with those at the lowest quintile of intake (median intake of 1.3 mg daily). A significant inverse association with MI was also found for vitamin B_{12}; the inverse association with MI was marginal for folate. The mechanism of action of the vitamin B_6 effect was unclear. It is clear, however, that further research is needed and warranted before the lingering question whether or not vitamin B_6 possesses antiatherogenic activity can be satisfactorily answered.

There was a report in 1985 that a topical application of pyridoxal produced significant regression in the metastatic melanoma of two patients. Greater than 50% regression of lesions was noted after two weeks of treatment. Untreated lesions did not regress. This preliminary report needs follow-up.

Vitamin B_6 is an effective treatment for seizures in infants caused by a specific inborn metabolic disorder. Deficiencies in vitamin B_6 have been associated with a number of neurologic and behavioral disorders, but interventive data are largely lacking. There is a study of Egyptian mothers and their infants significantly relating the vitamin B_6 nutritional status of the mother to infant behavior. Some studies have indicated that, even in the United States, a significant percentage of women of child-bearing age, as well as pregnant and lactating women, may have vitamin B_6 intakes below the recommended dietary allowance.

Studies are needed to determine the effects of low maternal vitamin B_6 intake on neurologic and behavioral development in offspring: Experiments with vitamin B_6-deficient maternal rats have demonstrated effects that might impair developmental processes related to learning and memory in offspring.

Vitamin B_6 plays an active role in the immune system. Even marginal deficiency, such as is found in many of the elderly, may result in some immune deficits. Chronically ill patients, notably those with HIV-disease, also often exhibit marginal or frank vitamin B_6 deficiency. Both humoral and cell-mediated immune responses have been shown to be impaired in those with vitamin B_6 deficiencies. Supplementation to normal levels generally restores immune function due to deficiency. Higher doses have not been reported to further stimulate or modulate the immune system.

In one study, approximately one-third of a healthy elderly population had marginal vitamin B_6 deficiency. Supplementation with the vitamin in elderly subjects has produced significant improvement in immune function as determined by a number of laboratory measures, including lymphocyte proliferative responses to both T- and B-cell mitogens. Percentages of CD3+ and CD4+ (but not CD8+) cells increased significantly in elderly subjects receiving 50 milligrams of vitamin B_6 daily.

Vitamin B_6 has been used with some success as an antiemetic in a dose range of 50-200 milligrams daily. It has been effective in treating nausea subsequent to radiotherapy and nausea associated with pregnancy ("morning sickness"). In one double-blind trial, vitamin B_6 alleviated the severe nausea and significantly reduced the vomiting of those who received the vitamin in 25 milligram doses every eight hours for three days.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Vitamin B_6 is contraindicated in those hypersensitive to any component of a vitamin B_6-containing product.

PRECAUTIONS

Pre- and postnatal vitamin/mineral supplements typically deliver vitamin B_6 (as pyridoxine) at a dose of between 2 to 20 milligrams daily. Pregnant women and nursing mothers should avoid doses of vitamin B_6 greater than these doses, unless higher doses are prescribed by their physicians.

Those who are being treated with levodopa without concurrently taking carbidopa should avoid doses of vitamin B_6 of 5 milligrams or greater daily.

The use of vitamin B_6 for the treatment of vitamin B_6 deficiency, for the prophylaxis of isoniazid-induced peripheral neuropathy, for the treatment of vitamin B_6-dependency disorders (see Indications) or for the treatment of any other medical condition requires medical supervision.

ADVERSE REACTIONS

Doses of vitamin B_6, typically in the form of pyridoxine, of up to 200 milligrams daily are generally well tolerated. One report showed severe sensory neuropathy in seven adults after pyridoxine intakes that started at 50 to 100 milligrams/day and were steadily increased to 2 to 6 grams/day over 2 to 40 months. None of the subjects in the report showed sensory neuropathy at doses of pyridoxine of less than 2 grams/day. There is one report of a woman who had been taking 200 milligrams/day of pyridoxine for 2 years without showing sensory neuropathy who developed sensory neuropathy after she increased her pyridoxine dose to 500 milligrams/day. There are rare reports of sensory neuropathy occurring at pyridoxine doses in the range of 100 to 200 milligrams/day. The Food and Nutrition Board of the Institute of Medicine of the U.S. National Academy of Sciences has concluded that reports and studies showing sensory neuropathy at doses of pyridoxine less than 200 milligrams/day are weak and inconsistent, with the weight of evidence indicating that sensory neuropathy is unlikely to occur in adults taking pyridoxine at doses less than 500 milligrams/day.

Other adverse reactions reported with high doses of pyridoxine, include nausea, vomiting, abdominal pain, loss of appetite and breast soreness. Rare cases of pyridoxine-induced photosensitivity have been reported.

INTERACTIONS

DRUGS

Amiodarone: Concomitant use of vitamin B_6 and amiodarone may enhance amiodarone-induced photosensitivity reac-

tions. Doses of vitamin B_6 greater than 5-10 milligrams/day should be avoided by those taking amiodarone.

Carbamazepine: Chronic use of carbamazepine may result in a significant decrease in plasma pyridoxal 5'-phosphate levels.

Cycloserine: Cycloserine may react with pyridoxal 5'-phosphate to form a metabolically inactive oxime, which may result in a functional vitamin B_6 deficiency.

Ethionamide: The use of ethionamide may increase vitamin B_6 requirements.

Fosphenytoin: High doses of vitamin B_6 may lower plasma levels of phenytoin. Fosphenytoin is a prodrug of phenytoin.

Hydralazine: The use of hydralazine may increase vitamin B_6 requirements.

Isoniazid: (isonicotinic acid, INH). Isoniazid reacts with pyridoxal 5'-phosphate to form a metabolically inactive hydrazone, which may result in functional vitamin B_6 deficiency.

Levodopa: Concomitant use of levodopa and vitamin B_6 in doses of 5 milligrams or more daily may reverse the therapeutic effects of levodopa. Vitamin B_6 does not reverse the therapeutic effects of levodopa if levodopa is taken concurrently with the levodopa decarboxylase inhibitor carbidopa. Levodopa is typically administered as a combination product with carbidopa.

Oral contraceptives: The use of oral contraceptives may increase vitamin B_6 requirements. This was more the case with the older oral contraceptive agents with high-dose estrogen/progestin. It appears to be less the case with the newer low-dose estrogen/progestin products.

Penicillamine: Penicillamine may react with pyridoxal 5'-phosphate to form a metabolically inactive thiazolidine, which may result in a functional vitamin B_6 deficiency.

Phenelzine: Phenelzine may react with pyridoxal 5'-phosphate to yield a metabolically inactive hydrazone compound.

Phenobarbital: High doses of vitamin B_6 may lower plasma levels of phenobarbital.

Phenytoin: High doses of vitamin B_6 may lower plasma levels of phenytoin.

Theophylline: Theophylline may react with pyridoxal 5'-phosphate leading to low plasma levels of the coenzyme. This may increase the risk of theophylline-induced seizures.

Valproic acid: Chronic use of valproic acid may result in a significant decrease in plasma pyridoxal 5'-phosphate levels.

FOODS

Alcoholic beverages: Alcohol may increase the catabolism of pyridoxal 5'-phosphate. Chronic and excessive use of alcoholic beverages can result in vitamin B_6 deficiency.

OVERDOSAGE

No reports.

DOSAGE AND ADMINISTRATION

Vitamin B_6 is available in nutritional supplements principally in the form of pyridoxine hydrochloride. Pyridoxal 5'-phosphate is also available as a nutritional supplement. Pyridoxine hydrochloride is available in multivitamin and multivitamin/multimineral products as well as products that, in addition to vitamins and minerals, contain other nutritional substances. Single ingredient pyridoxine products are also available. Some products are available which contain mixtures of pyridoxine hydrochloride and pyridoxal 5'-phosphate. Typical doses of pyridoxine used for nutritional supplementation range from 2 to 20 milligrams/day.

Those who use pyridoxine for the management of premenstrual syndrome, typically use doses ranging from 50 to 100 milligrams/day. Those who use pyridoxine for the management of carpal tunnel syndrome, typically use doses ranging from 100 to 200 milligrams/day.

The Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences has recommended the following Dietary Reference Intakes (DRI) for vitamin B_6:

Infants	Adequate Intakes (AI)
0 through 6 months	0.1mg/day ~ 0.014 mg/Kg
7 through 12 months	0.3 mg/day ~ 0.033 mg/Kg
Children	**Recommended Dietary Allowances (RDA)**
1 through 3 years	0.5 mg/day
4 through 8 years	0.6 mg/day
Boys	
9 through 13 years	1.0 mg/day
14 through 18 years	1.3 mg/day
Girls	
9 through 13 years	1.0 mg/day
14 through 18 years	1.2 mg/day
Men	
19 through 50 years	1.3 mg/day
51 through 70 years	1.7 mg/day
Older than 70 years	1.7 mg/day
Women	
19 through 50 years	1.3 mg/day
51 through 70 years	1.5 mg/day
Older than 70 years	1.5 mg/day

Pregnancy	
14 through 50 years	1.9 mg/day
Lactation	2.0 mg/day

The DV (Daily Value) for vitamin B_6 (pyridoxine and related compounds), which is used for determining the percentage of nutrient daily values on nutritional supplement and food labels, is 2.0 mg. This is based on the U.S. RDA for vitamin B_6.

The Food and Nutrition Board has identified a Lowest-Observed-Adverse-Effect Level (LOAEL) for vitamin B_6 of 500 milligrams/day (See Adverse Reactions) and a No-Observed-Adverse-Effect Level (NOAEL) of 200 milligrams/day. Based on the NOAEL and an uncertainty factor of 2, the Food and Nutrition Board has recommended the following Tolerable Upper Intake Levels (UL) for vitamin B_6:

Infants	UL
0 through 12 months	ND
Children	
1 through 3 years	30 mg/day of vitamin B_6 as pyridoxine
4 through 8 years	40 mg/day of vitamin B_6 as pyridoxine
9 through 13 years	60 mg/day of vitamin B_6 as pyridoxine
Adolescents	80 mg/day of vitamin B_6 as pyridoxine
Pregnancy	
14 through 18 years	80 mg/day of vitamin B_6 as pyridoxine
19 years and older	100 mg/day of vitamin B_6 as pyridoxine
Lactation	
14 through 18 years	80 mg/day of vitamin B_6 as pyridoxine
19 years and older	100 mg/day of vitamin B_6 as pyridoxine
Adults	
19 years and older	100 mg/day of vitamin B_6 as pyridoxine

ND = Not Determinable

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Vitamin B_{12}

DESCRIPTION

The term vitamin B_{12} (cobalamin) is used in two different ways. Vitamin B_{12}, a member of the B-vitamin family, is a collective term for a group of cobalt-containing compounds known as corrinoids. The principal cobalamins are cyanocobalamin, hydroxocobalamin and the two coenzyme forms of vitamin B_{12}, methylcobalamin and 5-deoxyadenosylcobalamin (adenosylcobalamin). The term vitamin B_{12} is more commonly used to refer to only one of these forms, cyanocobalamin. Cyanocobalamin is the principal form of the vitamin used for fortification of foods and in nutritional supplements. In this monograph, vitamin B_{12} will be used in both ways. The meaning will be clear from its context. The cobalamins are comprised of a nucleotide (base, ribose and phosphate) attached to a corrin ring. The corrin ring is made up of four pyrrole groups and an atom of cobalt in its center. The cobalt atom attaches to a methyl group, a deoxyadenosyl group, a hydroxyl group or a cyano group, to yield the four cobalamin forms mentioned above.

Vitamin B_{12} is the most chemically complex of all the vitamins. It is also one of the most biologically interesting ones. Because of the striking dark red color of its crystals, vitamin B_{12} has been called "nature's most beautiful cofactor." Its close relatives hemoglobin, chlorophyll and the cytochromes are also brightly colored complex organometallic substances, which, along with vitamin B_{12} and some others derived from the parent molecule called uroporphyrinogen III, have led to their being known as the pigments of life. Vitamin B_{12} works in close partnership with folate in the synthesis of the building blocks for DNA and RNA synthesis as well as the synthesis of molecules important for the maintenance of the integrity of the genome. It is also essential for the maintenance of the integrity of the nervous system and for the synthesis of molecules which are involved in fatty acid biosynthesis and the production of energy. The human body does all of this with just two to three milligrams of the vitamin, which is much less than the weight of a tenth of a drop of water. It is even speculated that B_{12} was mainly responsible for the origin of the DNA world from the RNA world.

Deficiency of vitamin B_{12} results in hematological, neurological and gastrointestinal effects. The hematological effects of the deficiency are identical to that of folate deficiency and are caused by interference with DNA synthesis. The hematologic symptoms and signs of B_{12} deficiency, include hypersegmentation of polymorphonuclear leukocytes, macrocytic, hyperchromic erythrocytes, elevated mean corpuscular volume (MCV), elevated mean corpuscular hemoglobin concentration (MCH, MCHC), a decreased red blood cell count, pallor of the skin, decreased energy and easy fatigability, shortness of breath and palpitations. The resulting anemia of B_{12} deficiency, as is the case of the anemia of folate deficiency, is a megaloblastic macrocytic anemia. However, in the context of a simultaneous iron deficiency anemia, which is a microcytic one, anemia secondary to B_{12} deficiency may not result in macrocytic erythrocytes.

The neurological effects of the vitamin deficiency may occur even in the absence of anemia. This is particularly true in those who are over 60 years old. Vitamin B_{12} deficiency principally affects the peripheral nerves, and in later stages, the spinal cord. The symptoms and signs of the neurological effects of B_{12} deficiency, include tingling and numbness in the extremities (particularly the lower extremities), loss of vibratory and position sensation, abnormalities of gait, spasticity, Babinski's responses, irritability, depression and cognitive changes (loss of concentration, memory loss, dementia). Visual disturbances, impaired bladder and bowel control, insomnia and impotence may also occur. Gastrointestinal effects of B_{12} deficiency, include intermittent diarrhea and constipation, abdominal pain, flatulence and burning of the tongue (glossitis). Anorexia and weight loss are general symptoms of B_{12} deficiency. Recently, age-related hearing loss has been associated with poor vitamin B_{12} and folate status. Poor B_{12} status has also been associated with Alzheimer's disease.