

Vitamin B6 Supplements

Efficacy and Risk:Benefit Criteria

Preliminary Data from the
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Efficacy

For food supplements used for non-medicinal purposes (ie. to supplement the diet), the concept of efficacy relates to the product's ability to function in the manner which would be expected from it: in this case to prevent functional deterioration associated with insufficient dietary vitamin B6. Such deterioration can manifest in many and varied ways owing to this vitamin's role in numerous physiological and biochemical functions. Since individual manufacturers have different quality control standards, it is difficult for us to comment generally on the efficacy of the vitamin B6 products on the market. We understand that from time to time the Food Ministry conducts tests on product samples to ensure that quality standards are upheld, and we are aware of no adverse reports about the efficacy of individual vitamin B6 products.

Benefit

It is sometimes stated that no benefit exists for the use of supra-RDA dietary supplements, and therefore that any risk of toxicity, however small, is intolerable. However, supra-RDA vitamin B6 supplements are consumer products which have already been on the market for many years and are in considerable demand. As with any other consumer product associated with a small risk to health: household chemicals, garden pesticides, alcoholic drinks, fast motor vehicles and so on, the benefit is that perceived by the consumer. It would in fact be somewhat difficult to prove the benefit of any consumer product with scientific, referenced studies, and this is not normally requested. As far as supra-RDA food supplements are concerned, it is generally recognised that consumers take them because they feel better when they do than when they do not.

In the field of health promotion, the extraordinary variety of individuals who have been demonstrated to benefit from an increased consumption of vitamin B6, closely reflects the variety of physiological and biochemical functions which depend on an adequate intake of this vitamin, and suggests that many individuals are consuming sub-optimal levels. The degree of supplementation which may be required to normalise biochemical functions suggests that an individual's base-line requirements for this or other nutrients can be, or can become, markedly raised, perhaps as a result of an episode of severe nutritional depletion (Brown AS et al: Neurobiological plausibility of prenatal nutritional deprivation as a risk factor for schizophrenia. *J Nerv Ment Dis* 184(2):71-85. Susser E et al: Schizophrenia after prenatal famine. Further evidence. *Arch Gen Psychiatry* 53(1):25-31, 1996.)

One paper in particular suggests that vitamin B6 is marginally deficient in about 50% of pregnant women, and points out that studies have shown that supplementation with 20 mg pyridoxine daily may be necessary to keep the laboratory measurements of vitamin B6 (RBC glutamate-oxaloacetate transaminase) in the normal range (Heller S et al. Vitamin B6 status in pregnancy. *Am J Clin Nutr* 26(12):1339-48, 1973).

We are currently compiling references to numerous papers which have identified low vitamin B6 levels, compared with normals, in sufferers from a variety of diseases. The following vitamin B6 repletion studies also support the view that vitamin B6 insufficiency, to the degree necessary to cause functional impairment, is relatively common.

1. 20 hypertensive patients received pyridoxine hydrochloride 5 mg/kg body weight daily. After 4 weeks, the mean systolic BP fell from 167 to 153 mm Hg ($p < 0.01$) and the mean diastolic BP fell from 108 to 98 mm Hg ($p < 0.005$). Plasma levels of adrenaline and noradrenaline also fell significantly (Aybak M et al. Effect of oral pyridoxine hydrochloride supplementation on arterial blood pressure in patients with essential hypertension. *Arzneimittelforsch* 45:1271-3, 1995).
2. 434 patients with 1 or more of the following premenstrual symptoms: tension, irritability, depression, lethargy, lack of coordination, violent feelings, breast tenderness, headache, edema, bloating or acne

received vitamin B6 25-100 mg twice daily (adjusted by patients depending upon relief or side-effects) or placebo. While there was no significant difference in relief of any one symptom, overall improvement was noted in 82% of the B6 group compared to 70% of the placebo group ($p < 0.02$). Patients who took analgesics during the study were significantly less likely to benefit from either vitamin B6 or placebo (Williams MJ, Harris RI, Dean BC. Controlled trial of pyridoxine in the premenstrual syndrome. *J Int Med Res* 13:174-9, 1985).

3. 7 patients and 6 controls with bronchial asthma received 50 mg pyridoxine HCl twice daily. All asthmatics reported a dramatic decrease in the frequency, duration and severity of asthmatic attacks, and wheezing ceased in about 1 week, even though both plasma and erythrocyte pyridoxal phosphate levels only increased significantly in the controls (Reynolds RD, Natta CL. Depressed plasma pyridoxal phosphate concentrations in adult asthmatics. *Am J Clin Nutr* 41:684-8, 1985).
4. In a double-blind study on 76 asthmatic children, 100 mg vitamin B6 supplementation daily brought significant improvement and a reduction in the use of conventional medications. A dose of 50 mg per day was not effective. Collipp PJ et al: Pyridoxine treatment of childhood bronchial asthma. *Ann Allergy* 35(2):93-7, 1975.
5. 15 elderly persons aged 65-81, some of whom had low pre-supplement levels of pyridoxal-5-phosphate, received pyridoxine hydrochloride 50 mg daily or placebo. After 1-2 months, treated subjects showed significant increases in lymphocyte responses to mitogens and antigens, and percentages of T3+ and T4+ but not T8+ cells increased significantly (Talbot MC et al. Pyridoxine supplementation: Effect on lymphocyte responses in elderly persons. *Am J Clin Nutr* 46(4):659-64, 1987).
6. Autistic children receiving vitamin B6 for autism were either continued on vitamin B6 or given placebo, on a double-blind basis. The placebo group significantly deteriorated after withdrawal of the vitamin B6. Rimland B et al: The effect of high doses of vitamin B6 on autistic children: a double-blind crossover study. *Am J Psychiatry* 135(4):1978.
7. Questionnaires on the treatment of 4,000 autistic children revealed that among the biomedical treatments, the use of high-dosage vitamin B6 with magnesium was found to be 6 times more effective than the two commonly used pharmaceutical agents fenfluramine and thioridazine hydrochloride. Rimland H: Controversies in the treatment of autistic children: vitamin and drug therapy. *J Child Neurol* 3 Suppl:S68-72, 1988.
8. 18 consecutive studies since 1965 have been published on the role of high dosage vitamin B6 in autism, 11 of which were double-blind, placebo-crossover experiments, which show that benefits may occur in about half of all autistic children and adults. None of the studies showed any significant adverse effects although doses of up to 6,000 mg daily were used. Rimland B: Vitamin B6 in autism: The safety issue. *Autism Research Review International* 10(3):3, 1996. (Autism Research Institute, San Diego).
9. Plasma levels of vitamin B6 were found to be very low in 16 sickle cell anaemia sufferers compared with normals. Supplementation with 100 mg vitamin B6 per day resulted in an increase in number of red cells and haemoglobin. Natta CL et al: Apparent vitamin B6 deficiency in sickle cell anaemia. *Am J Clin Nutr* 40(2):235-9, 1984.
10. The status of vitamin B6 and other B vitamins was investigated in patients with cancers of the female reproductive system. It was found that (1) The more the carcinoma had progressed, the more pronounced was the impairment of vitamin B6, B1 and B2 activation tests. (2) Soon after the start of radiotherapy, a biochemical deficiency of vitamins B1 and B6 was provoked. (3) A similar reduction of vitamin B1 and B6 enzyme activities was observed after the administration of cytostatic drugs. (4) Vitamin A, C and E status was also impaired. (5) The 5-year survival rate was about 10-15% better in the groups which were administered vitamin B6 than the groups which did not. (6) Daily administration of 300 mg vitamin B6 supplements was required to prevent impairment of the biochemical parameters of vitamin B6 status. Ladner HA: Vitamin B6, cancer and irradiation. *Strahlenschutz Forsch Prax* 26:63-69, 1985.
11. Patients with bladder cancer and given BCG immunotherapy were randomized to receive multiple dietary supplements (vitamins A, B6, C and E plus zinc) in the RDA range or the megadose range. The recurrence of tumours measured at 10 months was found to be 91% in the RDA group and only 41% in the megadose group. Lamm DL et al: Megadose vitamins in bladder cancer: a double-blind clinical trial. *J Urol* 151(1):21-6, 1994.

12. In contraceptive pill users with depression, anxiety and other symptoms, vitamin B6 supplementation restores normal tryptophan metabolism and relieves the related symptoms. Bermond P: Therapy of side effects of oral contraceptive agents with vitamin B6. *Acta Vitaminol Enzymol* 4(1-2):45-54, 1982.
13. Vitamin B6 deficiency, with requirements greatly above normal (vitamin B6 "dependency") should be considered in any baby suffering from seizures that are hard to control. Crowell GF et al: Pyridoxine-dependent seizures. *Am Fam Physician* 27(3):183-7, 1983.
14. In 16 kidney stone sufferers supplemented with magnesium and vitamin B6, there was a significant decline in the excretion of oxalate, leading to a significant decrease in kidney stone risk index after 120 days of treatment. Rattan V et al: Effect of combined supplementation of magnesium oxide and pyridoxine in calcium-oxalate stone formers. *Urol Res* 22(3):161-5, 1994.
15. Urinary oxalate excretion was significantly reduced in 12 kidney stone patients administered vitamin B6 supplements in doses of 250-500 mg daily. Mitwalli A et al: Control of hyperoxaluria with large doses of pyridoxine in patients with kidney stones. *Int Urol Nephrol* 20(4):353-9, 1988.
16. In a randomized double-blind crossover trial, the effectiveness of vitamin B6 supplementation at 50 mg per day for 3 months against premenstrual syndrome was compared with placebo in 63 women. The B6 group observed a significant beneficial effect on emotional symptoms: depression, irritability and fatigue. Doll H et al: Pyridoxine (vitamin B6) and the premenstrual syndrome: a randomized crossover trial. *J R Coll Gen Pract* 39(326):364-8, 1989.
17. Premenstrual acne improved in 72% of 106 women given vitamin B6 supplements. Snider BL et al. Pyridoxine therapy for premenstrual acne flare. *Arch Dermatol* 110:130-131, 1974.
18. Scores for mental performance were compared with levels of homocysteine (a marker of vitamin B12 deficiency) and serum levels of vitamins B6, B12 and folate, in 70 men aged 54-81. Lower levels of B12 and folate and higher levels of homocysteine were associated with poorer mental performance. Higher concentrations of vitamin B6 were related to better memory performance. Riggs KM et al: Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study. *Am J Clin Nutr* 63(3):306-14, 1996.
19. 617 patients diagnosed with premenstrual syndrome were randomized to treatment with vitamin B6 supplements or placebo in a double-blind trial. A global assessment after three cycles revealed significant improvement in the B6 group. Williams MJ et al: Controlled trial of pyridoxine in the premenstrual syndrome. *J Int Med Res* 13(3):174-9, 1985.

Safety

None of the above studies have identified any significant adverse reactions from the use of high-dose vitamin B6 supplements. It is important to acknowledge that reports of peripheral neuropathy after vitamin B6 supplementation which have arisen in the literature relate only to the pyridoxine form of supplementation. Pyridoxal-5-phosphate supplements have been available for some years, and are increasingly replacing pyridoxine in B6 products, but have not been linked with any form of toxicity. Nutritional medicine clinicians comment that the neurotoxicity is believed to be due to exceeding an individual's ability to phosphorylate pyridoxine to the active coenzyme, pyridoxal phosphate. The resulting high pyridoxine blood level could be directly neurotoxic or may compete for binding sites with pyridoxal phosphate resulting in a relative deficiency of the active metabolite (Parry GJ, Bredesen DE: Sensory neuropathy with low-dose pyridoxine. *Neurology* 35:1466-8, 1985; Waterston JA, Gilligan BS: Pyridoxine neuropathy. *Med J Aust* 146:640-2, 1987). Supplementation in the form of pyridoxal phosphate should thus avoid this danger.

Epidemiological criteria would appear to confirm the rarity of adverse effects from high-dose pyridoxine. We estimate that at least six companies in the UK are selling products containing 50-100 mg pyridoxine, and that their combined turnover is probably in excess of £20 million per annum. If each company markets 100 products, including one B6 x 50 mg product and one B complex x 50 mg product, this would, at a very rough estimate, suggest a turnover of £400,000 per annum in such products. However despite these sales figures, no cases of peripheral neuropathy as a result of pyridoxine supplementation were reported to the Medical Toxicology Unit during the five years of their recently completed monitoring study (Shaw D, Kolev S, Leon C et al: Toxicological problems resulting from exposure to traditional medicines and food supplements. Traditional Remedies Surveillance Project, Medical Toxicology Unit, Guy's & St Thomas' Hospital Trust, London).

Compared with the above data, the one study which reports peripheral neuropathy at doses as low as 50-100 mg pyridoxine (Dalton K, Dalton MJT: Characteristics of pyridoxine overdose neuropathy syndrome. Acta Neurol Scand 76:8, 1987) seems particularly anomalous. Peripheral neuropathy can, of course, have many other causes besides pyridoxine overdose, and product contamination cannot be ruled out. Vague neurological complaints are common among PMS sufferers and may be due to numerous causes. This uncontrolled study on patients who were simultaneously in an active multi-faceted treatment programme fails to demonstrate that symptom relief was due to stopping pyridoxine supplements. (Gaby AR. Editorial: Vitamin B6 toxicity: How much is too much? Townsend Letter for Doctors, May, 1988, p 184).

Conclusions

Since the peripheral neuropathy reported in the Dalton and Dalton study, if it was related to high-dose pyridoxine supplementation, appeared only after several years of supplementation, we agree that products with a potency of 50 mg or more should be labelled "Do not take for more than 6 months without professional advice". We also agree that an upper limit of 100 mg pyridoxine in vitamin B6 supplements should be considered.

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