COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON
VITAMIN B6 (PYRIDOXINE) TOXICITY

Introduction

1. We were asked to review the safety of vitamin B6, following concerns expressed about the potential toxicity of high dose dietary supplements. One vitamin B6 supplement was highlighted since a single dose contained 100 mg - more than 50 times the amount required to maintain normal bodily function. Dietary supplements, classified as foods, are freely available to the general public and are consumed by individuals who wish to supplement their diet. We note that vitamin B6 products with Marketing Authorizations (ie licensed as medicines) are also freely available under the General Sales List Order to individuals for the self-treatment of specific medical conditions. Other licensed vitamin B6 products, which contain higher doses, are available from pharmacies or on prescription from General Practitioners.

2. The generic term vitamin B6 includes six vitamers: the alcohol pyridoxine, the aldehyde pyridoxal, the amine pyridoxamine and their 5'-phosphates. At one time *pyridoxine* was used as a generic descriptor but since 1973, IUPAC-IUB and IUNS nomenclature has been used. This nomenclature is shown below. As can been seen, the vitamers are interconvertible.

Pyridoxine	⇄	**Pyridoxine phosphate**
		⇓
Pyridoxal	⇄	**Pyridoxal phosphate**
		⇑ ↓↑
Pyridoxamine	⇄	**Pyridoxamine phosphate**

3. Vitamin B6 is essential for good health and plays a major role in amino acid metabolism. Protein intake affects vitamin B6 requirements. For example, adults maintained on vitamin B6-deficient diets develop abnormalities in tryptophan and methionine metabolism faster and their blood vitamin B6 levels fall faster when they have a diet high in protein (approximately 80-160 g/day) in comparison with low protein intakes (30-50 g/day). During repletion of vitamin B6-deficient subjects, tryptophan and methionine metabolism and blood vitamin B6 levels are returned to normal faster at low levels of protein intake. The EC's Scientific Committee for Food and the UK

Government's Committee on Medical Aspects of Food Policy have both reported that 15µg vitamin B6 per gram protein per day is sufficient for the needs of healthy people. This approximates to a daily amount of between 1.1 mg and 1.5 mg for those with an average protein intake. Results of the National Food Survey (Ministry of Agriculture, Fisheries and Food 1995) show that the average amount of vitamin B6 in the diet of the population is sufficient to meet the estimated requirements.

4. Pyridoxal phosphate, one of the vitamers, is a coenzyme in transamination, deamination, decarboxylation and trans-sulphuration reactions within the body. Individuals with deficiencies in some enzymes such as cystathionine synthetase, cystathionase, peroxisomal glyoxylate amino transferase and glutamine decarboxylase, may show improvement following vitamin B6 administration. For example, homocystinuria, an autosomal recessive aminoacidopathy resulting from a defect in cystathionine β-synthase, is characterised by excessive homocysteine in plasma and urine. Plasma methionine levels are elevated and patients develop ectopia lentis, mental retardation, and hepatomegaly as well as deformities in the cardiovascular system and skeleton. Because of the many metabolic differences in individuals with this and other similar hereditary diseases, it is not appropriate to use the data from case studies of such patients receiving vitamin B6 medication when assessing the safety of vitamin B6 supplements sold as foods.

Human Toxicity Data

5. Severe sensory peripheral neuropathy in individuals following ingestion of large doses of vitamin B6 was first described in the early 1980s. Symptoms of toxicity include hyperaesthesia, paraesthesia, muscle weakness, numbness and loss of proprioception and vibration sense. Electrophysiological measurements and examination of nervous tissue by biopsy in some individuals have demonstrated nerve damage. The lowest dose reported to have been followed by symptoms consistent with sensory nerve damage is 50 mg per day (Dalton K, Dalton MJT. Acta Neurol Scand 1987; 76: 8-11). Signs of toxicity were observed after an average of 35 months. We are aware that the study by Dalton and Dalton has some methodological deficiencies but, nevertheless, the symptoms reported by the patients are consistent with the well described clinical syndrome of peripheral sensory neuropathy. The observations of Dalton and Dalton are also consistent with the reported symptoms of patients in other studies undertaken at higher doses which contained objective measures as well as subjective observations (eg. Berger AR, Schaumberg HH, Schroder C et al. Neurology 1992; 42: 1367-1370, Albin RL, Albers JW, Greenberg HS et al, Neurology 1987; 37: 1729-1732, Albin RL, Albers JW Neurology 1990; 40: 1319, Waterston JA, Gilligan BS 1987; 146: 640-642). In most instances, the clinical signs of toxicity were reversible once ingestion of high doses of vitamin B6 had ceased. However, in some instances where the dose of this vitamin was especially high, signs of damage remained. The clinical studies suggested an inverse relationship between the daily dosage and the time required before symptoms were detected. We consider that the small number of individuals involved and/or the short duration of administration may explain the absence of signs of sensory peripheral neuropathy in some studies. As stated above in paragraph 4, we consider that studies of individuals with hereditary diseases such as homocystinuria, are inappropriate in the assessment of vitamin B6 toxicity from dietary supplements.

Animal Toxicity Data

6. Several studies have shown that administration of high doses of vitamin B6 to different animal species, including the rat and dog, resulted in ataxia and muscle weakness. Neuropathological damage, including degeneration of the dorsal root ganglia, axonopathy and demyelination have been observed. The lowest reported adverse effect level in animals is 50 mg/kg bodyweight/day in the dog after approximately 16 weeks administration (Phillips *et al*. Toxicol Appl Pharmacol 1978; 44: 323). We are aware of a report of a no observed adverse effect level in the dog of 20 mg/kg bodyweight/day for 80 days (Unna. J. Exp Ther 1940; 70: 400), but, bearing in mind the age of the study and without further experimental detail, we have not used this figure in our consideration. With a safety factor of 300 (10 for the use of animal data, 10 for inter-individual human variation, 3 for the use of a lowest observed adverse effect level) and assuming that an individual weighs 60 kg, extrapolation from the lowest observed adverse effect level in dogs (50 mg/kg bw/day) would give a maximum daily safe dose for humans of 10 mg.

Conclusions

7. There is no doubt that consumption of vitamin B6 by humans in excess of the amount required to maintain bodily function can result in symptoms which are consistent with sensory peripheral neuropathy. Furthermore, the animal toxicity data are consistent with the study of Dalton and Dalton (1987) which reported adverse effects at daily intakes of 50 mg in humans. Electrophysiological measurement and examination of nerve tissue confirm neuropathological changes. With the exception of the instances where especially high doses (in the order of grams) of this vitamin were ingested by some individuals, the signs of toxicity are reversible after cessation of ingestion. The lowest dose reported to have adverse effects in humans is 50 mg per day; although there are methodological deficiencies in the study showing effects at this level of intake, we consider it would be unwise to ignore this evidence in the light of other supporting human and animal data.

Recommendation

8. Allowing for a margin of safety between the lowest observed adverse effect level in humans and bearing in mind the supporting animal toxicity data, we *recommend* that the maximum daily intake of vitamin B6 from dietary supplements should be 10 mg per day.

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