Vitamin B_6 (Pyridoxine)

Introduction

Vitamin B_6 is a water-soluble vitamin that is important in carbohydrate, lipid, and amino acid metabolism. It is found in the body in three primary forms: pyridoxine (the common name given mainly to the alcohol form, or pyridoxol); pyridoxal (the aldehyde); and pyridoxamine (the amine). The activated forms of pyridoxal and pyridoxamine are active coenzyme forms, and the interconversion between them is involved in many of the biological functions of vitamin B_6. This vitamin is extensively involved in the metabolism of nitrogen-containing compounds, including serotonin, dopamine, norepinephrine, gamma-aminobutyric acid (GABA), and the heme component of hemoglobin. Pyridoxine, as pyridoxal phosphate, also has an important role in the conversion of tryptophan to nicotinic acid.

Vitamin B_6 interacts with several drugs, which may either decrease the activity of the drug or increase the need for the vitamin or both. Individuals taking medications on a regular basis should discuss their vitamin B_6 status with their health care providers. Furthermore, several medical conditions, including autoimmune disorders, impaired renal function, and alcohol dependence, can increase the requirement for pyridoxine (Institute of Medicine [IOM] 1998; Bates 1999; Chiang 2005).

Safety Considerations

Both deficiency and excess of pyridoxine may produce neurological disturbances (Hathcock and Rader 1990). The first report of pyridoxine neurotoxicity in humans described a sensory neuropathy of the extremities in women with daily intakes of 2,000 to 6,000 mg, mostly taken in attempt to control premenstrual symptoms (Schaumburg et al. 1983). The neuropathy slowly and often incompletely regresses after cessation of the elevated dose (Albin et al. 1987; Albin and Albers 1990; Santoro et al. 1991). Most cases of sensory neuropathy have resulted from intakes of greater than 600 mg per day, but evidence suggests that for some individuals, neuropathy may

occur after doses as low as 300 to 500 mg (Parry and Bredesen 1985; Bendich and Cohen 1990; Hathcock and Rader 1990). At high intake levels, the total dose over time may give a better prediction of the potential for neurotoxic response than either the daily dose or the duration of the high intake (Bendich and Cohen 1990). This relationship, however, does not extend to low, nontoxic doses.

Treatment with either 150 or 300 mg of pyridoxine for up to 4 months did not produce signs of sensory neuropathy or any other adverse effects in 24 carpal tunnel syndrome patients (Del Tredici et al. 1985). Bernstein and coworkers (Bernstein and Lobitz 1988; Bernstein and Dinesen 1993), using physical neurological methods, found no evidence of neurological effects of pyridoxine at intakes of up to 200 mg per day over a period of 4 months. Most subjects showed no adverse effects at 150 to 200 mg per day supplemental intake (Del Tredici et al. 1985; Parry and Bredesen 1985; Bernstein and Lobitz 1988; Bernstein and Dinesen 1993). At intakes of 200 mg (but not at 150 mg), a few subjects experienced signs of adverse neurological effects such as sensory tingling and numbness (Parry and Bredesen 1985; Brush 1988). Consumption of 200 mg pyridoxine per day may decrease the time it takes for adverse effects to develop after higher levels are initiated (Parry and Bredesen 1985).

A double-blind, placebo-controlled study in which 100 or 500 mg of vitamin B_6 was consumed daily for 14 days showed marginal evidence of improvement in a digital coding test but also some evidence of an adverse effect on word recognition (Molimard et al. 1980); no further evidence to support either of these possible effects has been published. The apparent adverse effect was significant at a 500 mg intake level, but not at 100 mg.

There is strong controversy over the validity of the study reporting of adverse effects at daily pyridoxine intakes of around 100 mg or less (Dalton and Dalton 1987). The design of the study, which involved telephone interviews using leading questions, has raised questions about the validity of its observed effects. Although the Dalton and Dalton report has been cited as evidence that pyridoxine intakes below 100 mg per day can cause sensory neuropathy (European Commission's Scientific Committee on Food [EC SCF] 2000; Expert Group on Vitamins and

Minerals [EVM] 2003), the data showed an average intake of 117 mg per day among women with adverse symptoms and a nearly identical average intake (116 mg per day) in the control group. The group with reported symptoms had taken pyridoxine for a longer period of time—an average of 2.9 years, compared with 1.6 years for those without symptoms. Some women reporting adverse effects had intakes of 50 mg or less. Inaccuracies in the telephone survey method and a lack of objective neurological assessment are likely to have introduced bias. The symptoms observed had no dose-response relationship to pyridoxine intake, but they did show a time-response relationship. If the time-dose relationship were extended far enough it would lead to the conclusion that even deficient intakes would be "toxic" if taken long enough. The IOM concluded that the data were not of sufficient quality to warrant use in a risk assessment for pyridoxine (IOM 1998).

Some reports have suggested that high intakes of pyridoxine may carry risk of oxalate kidney stones, but these reports are problematic. The reported cases may have been associated with the drug pyridoxilate (a combination of pyridoxine and glyoxalate) (Daudon et al. 1987), and a recent prospective epidemiological study found the relative risk of oxalate renal stones to be decreased for men consuming more than 40 mg of pyridoxine in comparison with those consuming less than 3 mg (Curhan et al. 1996).

There seems to be no recent publications on the neurotoxic effects of pyridoxine, but there are many reports of this vitamin influencing the effects of toxic compounds, for example, cadmium (Wen et al. 2010).

Official Reviews

IOM (1998). The IOM identified a NOAEL of 200 mg from clinical data (Del Tredici et al. 1985; Bernstein and Lobitz 1988) but considered the Dalton and Dalton (1987) data too unreliable to serve as the basis of a UL. It thus applied a UF of 2 to the 200 mg human NOAEL, deriving a UL of 100 mg.

EC SCF (2000). While the EC SCF recognized the weaknesses of the Dalton and Dalton data, it considered the other available clinical data to be of marginal scientific quality as well. Consequently, it used the Dalton and Dalton data as the basis of its pyridoxine UL, dividing an intermediate LOAEL of 100 mg per day by a composite UF of 4. This 100 mg LOAEL was formulated from the intakes of the Dalton and Dalton group with adverse effects, which consumed a mean intake of 117 mg and a median intake of <100 mg. (The Dalton and Dalton report asserted that some individuals with minor adverse effects had taken only 50 mg per day, but this was not factored into the EC SCF LOAEL.) The composite UF of 4 resulted from assigning a factor of 2 to account for long-term intakes and a further factor of 2 to allow for deficiencies in the database. The EC SCF UL of 25 mg per day that resulted from the selected LOAEL and UFs was justified by the absence of any reports, even anecdotal ones, of adverse effects at intakes of 25 mg per day.

EVM (2003). The UK's EVM, concluding that the available human data were inadequate, based their assessment on a study that found a LOAEL of 50 mg per kg body weight per day in dogs (Phillips et al. 1978). They extrapolated the dog data to a 60-kg human adult representative weight by applying a composite UF of 300 to derive an SUL of 10 mg per day. The composite factor represented a factor of 3 for LOAEL-to-NOAEL extrapolation, a factor of 10 for interspecies extrapolation, and another factor of 10 for variation in human sensitivity.

In summary, these three government reports based their risk assessment on widely differing datasets and methods, especially in determining uncertainty. The result is that the daily amounts of pyridoxine considered safe differ significantly: 100 mg for the IOM, 25 mg for EC SCF, and 10 mg for the EVM. These disparate outcomes suggest that better data selections and uncertainty assessment are needed and that current corresponding UL values are somewhat arbitrary.

CRN Recommendations

The complete absence of adverse effects in credible, well-designed studies at 100 and 150 mg and only marginal evidence of adverse effects at 200 mg (Parry and Bredenson 1985; Brush

1988) indicate that 100 mg can be confidently identified, with a low level of uncertainty, as a safe level of consumption. Consequently, CRN identifies the supplemental intake NOAEL for pyridoxine to be 100 mg. Intakes from conventional foods alone are generally below 3 mg (IOM 1998; EVM 2003), and thus this source does not meaningfully contribute to safety concerns. CRN's UL is 100 mg, but somewhat higher amounts may be safe for most people and/or for shorter periods of time.

Quantitative Summary for Vitamin B_6 (Pyridoxine)

CRN UL, supplemental intake	100 mg/day
IOM UL, total intake	100 mg/day
EC SCF UL, total intake	25 mg/day
EC supplement maximum	Not determined
EVM SUL, supplemental intake	10 mg/day

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