Vitamin B6 and neuropathy-an update

Introduction

Vitamin B6, a water-soluble vitamin, plays a crucial role in various bodily functions, including amino acid metabolism, hormone regulation, blood formation, immune function, and nerve health. It is found in a variety of foods such as meat, fish, eggs, dairy products, grains, and vegetables. Vitamin B6 can occur in 6 forms (the so-called B6 vitamers): pyridoxine, pyridoxal or pyridoxamine and the phosphorylated derivatives pyridoxine phosphate, pyridoxal phosphate and pyridoxamine phosphate. The active form of vitamin B6 is pyridoxal 5'-phosphate (PLP). The body converts dietary forms of vitamin B6 (such as pyridoxine, pyridoxal, and pyridoxamine) into PLP for use in these essential metabolic processes(1).

The recommended daily allowance (RDA) of vitamin B6 for men and women aged 14 and over is 1.5 milligrams. The Commodities Act regulations on the exemption of nutritional supplements state as of October 1, 2018 that food supplements contain a maximum of 21 mg vitamin B6 per daily amount to be consumed(2). In May 2023, a new European Food Safety Authority (EFSA) scientific opinion on the tolerable upper intake level (UL) for vitamin B6 was given, based on systematic reviews of the literature. In this scientific opinion the EFSA established an upper limit for vitamin B6 intake of 12 mg per day for adults(3).

Vitamin B6 deficiency is rare in the general population. Excessive intake over a long period can cause nerve damage, leading to peripheral neuropathy, a condition characterized by numbness, tingling, or severe nerve pain, especially in the hands and feet. Peripheral neuropathy affects more than 5% of adults over 50 years of age, with higher rates among older adults and those with underlying medical conditions. Causes of peripheral neuropathy include genetic factors, infections, metabolic disorders, exposure to toxins and systematic diseases. Studies have linked long-term, high-dose B6 supplementation to the development of peripheral neuropathy(4).

In the past, the Netherlands Pharmacovigilance centre Lareb has signalled the association between food supplements containing vitamin B6 and the occurrence of neuropathy and informed the Netherlands Food and Consumer Product Safety Authority (NVWA)(5, 6). Lareb continues to receive reports about this association and therefore an overview of the received reports is presented.

Reports

Index-case:
This spontaneous report from a consumer or other non-health professional concerns a female aged between 50-60 years, with paraesthesia of lower limbs following administration of vitamin supplement Solgar VM 75* (containing 7,5mg vitamin B6 per daily dose of 1 tablet) for supplementation therapy with a latency of 15 months after start. The blood level of vitamin B6 was 1100nmol/l. The patient is recovering after withdrawal. The patient has no medical history. The patient has no past drug therapy.

All reports
In the period from August 2007 until July 2024 Lareb received 238 reports of neuropathic pain associated with the use of food supplements containing vitamin B6. 181 reports (76%) concerned women, 57 reports (24%) concerned men. Median age was 53 years and ranged from 3 to 92 years.

Mean latency was 5 months and ranged from 'minutes after start' to 37,5 years. Blood levels of vitamin B6 were reported in 90 reports and ranged from 87 to 4338 nmol/L (median 500 nmol/L). Reference values vitamin B6: 35-200 nmol/L(7). 84 patients were recovered/recovering after withdrawal of the food supplement (positive dechallenge). Four patients reported the same complaints after starting the food supplement again (positive rechallenge).

In 97 reports patients reported the use of concomitant medication. Most reported comedication and information about frequency of neuropathy mentioned in the Summary of Product Characteristics (SmPC) of the concomitant medication is shown below:

Concomitant medication	**Number**	**SmPC**
metoprolol	7	Paraesthesia (rare)
cholecalciferol	7	-
omeprazole	6	Paraesthesia (uncommon)
simvastatin	6	Paraesthesia (rare)
acetylsalicylic acid	5	-
pantoprazole	5	Paraesthesia (frequency unknown)
paracetamol	4	-
Ascorbic acid	4	-
calcium with vitamin d	4	-
salbutamol	4	-

Besides concomitant medication also underlying illness can play a role in the occurrence of neuropathy. Potential other causes mentioned in the reports are: diabetes mellitus (n=2), fibromyalgia (n=1), gout (n=1), alcohol abuse (n=1), Lyme disease (n=1), polymyalgia (n=1), encephalomyelitis and transient ischemic attack (n=1), radiotherapy (n=1), small fibre neuropathy (n=1), vitamin D deficiency (n=1) and osteoarthritis (n=1).

In 160 reports the dose of vitamin B6 is known. The vitamin B6 dose in these reports ranges from 0,35 to 300 mg vitamin B6 per day.

Reports dose ≤21 mg

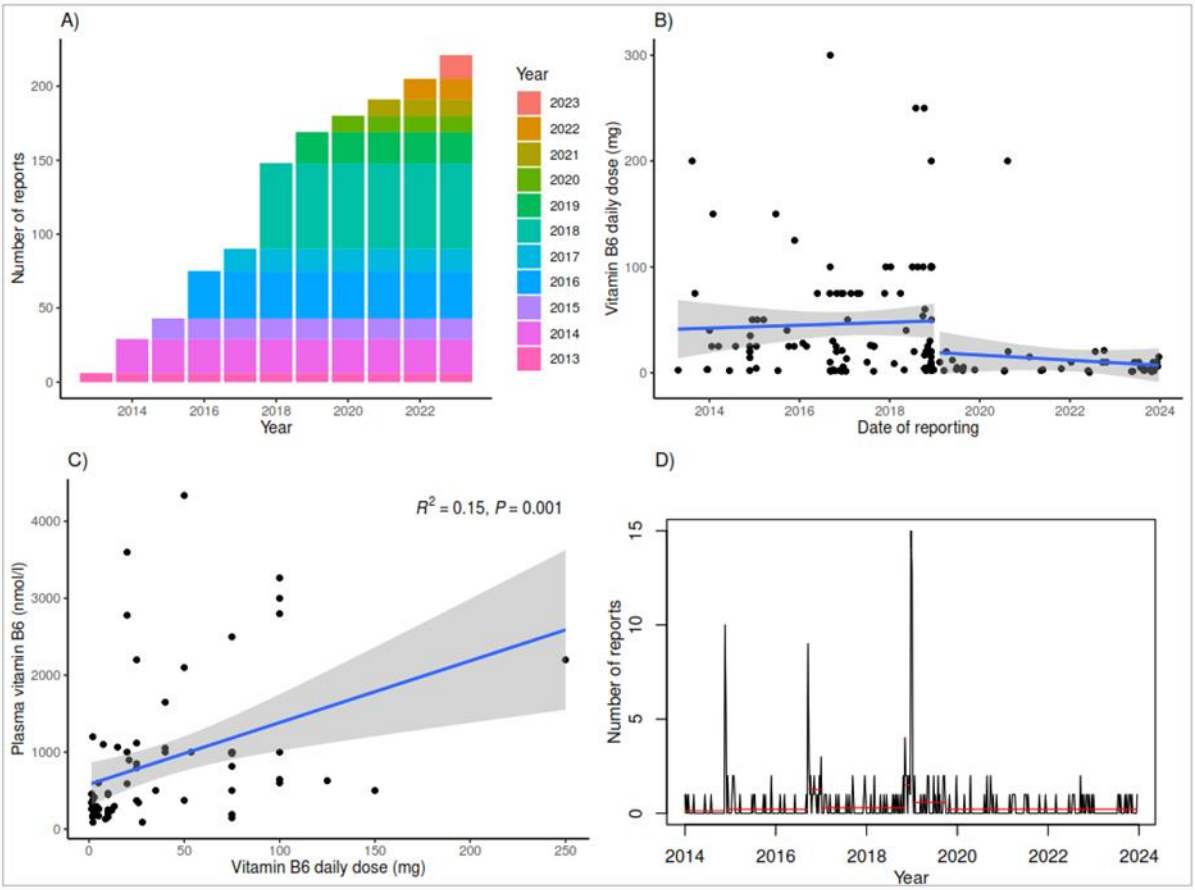
In 100 reports the dose of vitamin B6 is ≤21 mg per day. Of these 100 reports with a dose of vitamin B6 of ≤21 mg per day, 79 reports mention a dose of vitamin B6 of ≤12 mg per day.

Of the 100 reports with a dose of vitamin B6 of ≤21 mg per day, 95 reports were reported by consumers, 4 reports by physicians and 1 report by a pharmacist. The majority of the reports concern women (n=79), 21 reports concern men. The vitamin B6 dose ranged from 0,35 to 21 mg per day (median dose vitamin B6 is 4,1 mg/day, mean dose vitamin B6 is 7,2 mg/day). The median age is 52 years and ranges from 3 to 80 years. Latency varies from 'right after start' to 23 years (median latency 100 days). In 37 reports the user is recovered/recovering after withdrawal or dose reduction of the food supplement. In 43 out of the 100 reports the blood level of vitamin B6 is known. This ranged from 87 to 3600 nmol/L (median 296 nmol/L). Reference values vitamin B6: 35-200 nmol/L(7). Other factors reported that could have caused the neuropathic pain in these 100 reports with a dose of vitamin B6 of ≤21 mg per day are diabetes mellitus (n=1), radiotherapy (n=1), small fibre neuropathy (n=1) and vitamin D deficiency (n=1).

Reporting after dose maximization

We checked if there was an effect of the regulatory action in 2018 on maximum daily dosage for vitamin B6 on the reporting pattern of neuropathy associated with food supplements containing vitamin B6 to Lareb. It was seen that there is no prominent decline in the number of reports on neuropathy after the regulatory action in 2018 (Figure A). However, since the regulatory action for dose maximization from October 2018, very few reports are about higher dosages (Figure B). There was a weak correlation between daily dose and plasma levels of vitamin B6. Only 15% of the variability in the reported plasma levels could be explained by the daily dose (Figure C). Especially around some peaks in the reporting pattern, for instance in 2018, changepoints could be detected. However, from the second half of 2019 the number of reports per time period is lower and no change points were detected (Figure D).

Figure A: Cumulative number of reports of neuropathy associated with vitamin B6 exposure per year. Figure B: Scatterplot of the daily vitamin B6 dose in relation to the time of reporting. Blue lines are linear trend lines. Figure C: Scatterplot of plasma vitamin B6 levels in relation to the daily dose. Figure D: Changepoint analysis for reports of neuropathy related to vitamin B6 exposure. Changes in the red lines indicate changepoints.



Other sources of information

Literature

Muhamad et al conducted a systematic, computer-based search using the PubMed database. They included twenty articles in their review. They showed that elevated levels of vitamin B6, often

resulting from the use of dietary supplements, may lead to the onset of primarily, if not solely, sensory axonal neuropathy. Patients experiencing this condition often report subjective symptom improvement after stopping pyridoxine. While low vitamin B6 levels can be observed in individuals with peripheral neuropathy from various causes, there is no conclusive evidence that low B6 levels directly cause peripheral neuropathy. Many studies indicate that patients with peripheral neuropathy from different aetiologies experience subjective improvements in their neuropathy symptoms after receiving B6 supplementation; however, there is no data supporting the use of B6 as a standalone treatment—it is typically administered as part of a combination therapy alongside other vitamins. As such, the potential therapeutic role of B6 remains unconfirmed to date. Additionally, supplementation with vitamin B6, even as part of a multivitamin regimen, has not been shown to be harmful at allowable daily doses in patients already diagnosed with peripheral neuropathy. They conclude that current scientific evidence supports a neurotoxic role of B6 at high levels. Although some studies suggest that low B6 is also a potential risk factor, further studies in this area are needed(4).

Mechanism

Hadtstein and Vrolijk propose a plausible mechanism of pyridoxine toxicity in which recent research of hereditary neuropathy due to mutations in pyridoxal kinase (PDXK) provides insight. Genetic deficiencies in PDXK lead to the development of axonal sensory neuropathy. High levels of pyridoxine may lead to a similar condition via the inhibition of PDXK. Although the exact mechanism of PDXK-induced neuropathy is unclear, there are indications it involves disruptions in γ-aminobutyric acid (GABA) neurotransmission. Inhibiting PDXK reduces GABA synthesis and can cause convulsions. Notably, individuals with PDXK deficiency don't exhibit central nervous system (CNS) symptoms, likely because PDXK activity is preserved in the brain. Since pyridoxine poorly crosses the blood-brain barrier, its toxic effects are confined to peripheral tissues like sensory neurons. Disruption of GABA in these neurons may lead to excitotoxicity and nerve degeneration, causing peripheral neuropathy. This suggests that PDXK inhibition and consequently impaired GABA neurotransmission is the most plausible mechanism of pyridoxine toxicity(8).

Discussion and conclusion

Lareb still receives reports of peripheral neuropathy associated with the use of supplements with a lower dose of vitamin B6 than the maximum permitted dose in supplements of 21 mg/day. Perhaps the long-term use of some people also plays a role in the development of peripheral neuropathy. Pyridoxine accumulates in plasma after chronic use of supplements in some individuals. Furthermore, interindividual differences in the pharmacokinetics of vitamin B6 exist. These differences might explain different individual sensitivity to vitamin B6 toxicity(9). There are some limitations of the Lareb data regarding the information about the dose of vitamin B6 that was consumed. Previous studies have demonstrated that not only the dosage of vitamin B6 but also the specific vitamer present in dietary supplements plays a key role in the development of neuropathy(9). Unfortunately, this information is missing from many reports in the Lareb database. Furthermore, declared dosages on dietary supplements may not always be accurate, and it is often unclear how many doses were taken by the patients. Also, information about the dietary intake of vitamin B6 was not available. Given the potential risk, caution is advised regarding vitamin B6 supplementation.

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