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ORIGINAL RESEARCH ARTICLE

Vitamin B_6 in Health Supplements and Neuropathy: Case Series Assessment of Spontaneously Reported Cases

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Abstract

Introduction In the literature, vitamin B_6 has been linked to the development of polyneuropathy. Most often, these complaints were seen when taking high doses of vitamin B_6 for a long time. Evidence as to whether a lower dosage range of vitamin B_6 (< 50 mg/day) can also induce neuropathy is scarce.

Objective We aim to comprehensively describe the cases of neuropathy associated with vitamin B_6 received by the Netherlands Pharmacovigilance Centre Lareb and to assess the case series concerning the use of vitamin B_6 and neuropathic complaints.

Methods We describe the number and nature of the reported cases, including suspect product, dosage, duration of use, and vitamin B_6 serum levels. In addition, we describe the causality for the individual cases (Naranjo Probability Scale) and for the entire case series (Bradford Hill criteria).

Results In total, 90 reports on products containing vitamin B_6 included at least one adverse drug reaction in the standardized Medical Dictionary for Regulatory Activities (MedDRA®) query (SMQ; broad) 'peripheral neuropathy'. The amount of vitamin B_6 in the products varied between 1.4 and 100 mg per tablet. The serum vitamin B_6 level was known in 36 cases (88–4338 nmol/l), and the mean serum vitamin B_6 level was 907 nmol/l. However, no statistical correlation between dosage and vitamin B_6 blood levels was found.

Discussion and Conclusion Causality assessment of the case series of 90 reports to Lareb shows it is plausible for the vitamin B_6 supplements to have caused complaints such as neuropathies. This is especially the case with higher dosages and prolonged use, but dosages < 50 mg/day also cannot be excluded.

Key Points

Many vitamin supplements on the market contain a vitamin B_6 dosage higher than the maximum acceptable intake of 25 mg for adults. The literature describes neuropathic complaints with long-term use (months to years), most often for dosages from > 50 mg/daily to multiple grams daily.

A case series of 90 Dutch spontaneous reports indicates that prolonged use (mean latency 2.2 years) of vitamin B_6, most often in dosages higher than the maximum acceptable intake of 25 mg for adults, is associated with neuropathic complaints.

1 Introduction

Vitamin B_6 is a water-soluble vitamin that functions as a coenzyme in many reactions involving amino acids, carbohydrates and lipid metabolism. The major vitamers of vitamin B are pyridoxine, pyridoxal, pyridoxamine and

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their phosphorylated derivatives pyridoxine 5′-phosphate (PNP), pyridoxal-5′-phosphate (PLP) and pyridoxamine-5′-phosphate (PMP) [1].

A Dutch National Food Consumption survey in the Netherlands showed that the intake of vitamin B_6 was sufficient in the whole population in the period 2007–2010 [2]. However, on an individual level, deficiencies in vitamin B_6 may arise from insufficient intake or malabsorption or because of drugs such as isoniazid that inhibit enzymes involved in the metabolism of PLP, the active vitamer of vitamin B_6 [3, 4]. Certain groups, such as the elderly or patients with alcoholism, might have low vitamin B_6 blood levels [5]. Many hospitals in the Netherlands use 51–183 nmol/l as the reference values for vitamin B_6 blood levels [6].

Although vitamin deficiency is rare in the Netherlands [2], 27–56% of the study population in the previously mentioned Dutch Food Consumption survey reported the use of dietary supplements such as vitamins. About half of women aged $\geq$ 19 years used dietary supplements [2].

The recommended daily allowance for vitamin B_6 for men and women aged 19–50 years in the Netherlands is 1.5 mg if daily protein intake is 100 g [7]. The maximum acceptable intake is 25 mg for adults [7, 8].

In the literature, vitamin B_6 has been linked to the development of polyneuropathy [9–12]. Most often, these complaints were seen when high doses of vitamin B_6 were used for a longer period of time [1, 11, 12]. A review of the literature stated that vitamin B_6 used for $>$ 6 months and at doses $>$ 50 mg/day is probably harmful [13]. Evidence as to whether a lower dosage range of vitamin B_6 ($<$ 50 mg/day) can also induce neuropathy is scarce.

The Netherlands Pharmacovigilance Centre Lareb has received 90 reports on neuropathy associated with vitamin B_6, for a range of products with a variety of vitamin B_6 levels. Most vitamin products on the Dutch market are not registered as drugs through the Dutch Medicines Evaluation Board (MEB) but are governed by the Dutch Commodities Act. Lareb shares the reported adverse reactions related to these products with the Netherlands Food and Consumer Product Safety Authority (NVWA) [14]. Earlier pharmacovigilance activities led to multiple signals on the relation between vitamin B_6 in food supplements and neuropathic complaints, which were communicated to the NVWA [15, 16]. The aim of this article is to comprehensively describe the cases received and assess the case series concerning the use of vitamin B_6 and neuropathic complaints.

2 Methods

2.1 Selection of Cases

We studied all adverse drug reactions (ADRs) related to neuropathy and health supplements that contain vitamin B_6 reported to Lareb from 1991 (establishment of the center) until July 2017. Reports in the Dutch spontaneous database are coded using Medical Dictionary for Regulatory Activities (MedDRA®) codes [17] and individually assessed for causality by trained assessors. All (multi)vitamin products containing vitamin B_6 were selected and included for review if they contained an ADR coded with a MedDRA preferred term (PT) within the MedDRA version 20.1 standardised MedDRA query (SMQ) 'peripheral neuropathy' (broad) [18]. This SMQ can be used to select ADRs related to impairment of the peripheral motor, sensory and autonomic nervous system.

2.2 Description of the Cases

We describe the number and nature of the reported cases, including suspect product with dosage and duration of use, latency period, comedication, age and sex of the patient, seriousness of the ADR according to Council for International Organizations of Medical Sciences (CIOMS) criteria [19], de- and rechallenge information and vitamin B_6 serum levels. The correlation between milligrams of vitamin B_6 in the products and serum vitamin B_6 levels was assessed using a Pearson correlation coefficient.

In addition, we describe the causality for both the individual cases and the entire case series. The causality of cases received by Lareb is assessed on a case-by-case manner, which also includes documenting the score on the Naranjo Probability Scale [20], a quantitative tool used to estimate the likelihood that an ADR is actually due to the drug; these scores are given for the reports.

2.3 Causality of the Case Series

We assessed the case series using the Bradford Hill criteria [21]. These criteria included the strength of the association, consistency of the cases, specificity of the association, temporality, dose–response relationship, plausibility of the association, coherence, experiment and analogy.

In terms of strength of the association, the larger the association between exposure and risk, the greater the likelihood of the association being causal [22]. It is not possible to calculate an incidence or risk when using a spontaneous reporting database. An approximation for the strength of the association is calculating the disproportionality of the reported association in the database, which

can be determined in multiple ways. Unfortunately, the manner of coding means it is not possible to distinguish separate health supplements and it is therefore not possible to calculate disproportionality in the Lareb database. Therefore, we used the global database Vigibase® instead, in which health supplements are coded separately. We obtained numbers of reports and information component (IC) values for the selected PTs through Vigilyze®, a search and analysis tool (available to countries that are members of the World Health Organization [WHO] Programme for International Drug Monitoring). IC_{025} is the lower end of a 95% credibility interval for the information component. A positive IC_{025} value is the traditional threshold used in statistical signal detection at Uppsala Monitoring Centre (UMC); we therefore used these values as an indicator for disproportionality [23, 24].

The consistency of the association in the Lareb database with previous findings in other sources was assessed by reviewing the literature on this topic and comparing the spontaneous cases from the Dutch pharmacovigilance database with those from the literature. A structured literature search was conducted using a text search in PubMed, with the keywords vitamin B_6, pyridoxine, and neuropathy. There was no restriction on the time of publication nor initially on language, and only studies in humans were selected. This yielded an initial list of 189 articles. We checked whether known key publications were identified with this search. Publications were selected based on the title of the publication and keywords (n = 40 in total). One article was thereafter excluded because it was only available in Japanese. Abstracts of the remaining identified studies and case reports were then assessed for relevance to the scope of the review. We also checked the references of key publications to obtain articles not found with our previous search. The full paper was obtained for each study being considered for inclusion in the review.

3 Results

3.1 Description of the Cases

A total of 139 reports on food supplements/multivitamin products containing vitamin B_6 were selected. Of these, 90 reports contained at least one ADR in the SMQ 'peripheral neuropathy'. In the reports, 18 patients were male (20%) and 72 were female (80%). Mean age was 53.2 ± standard deviation (SD) 15.7 years; range 3–85. In total, 14 cases were serious according to CIOMS criteria, mainly because of the disabling character of the ADR (see Fig. 1).

The latency period was known in 57 cases. The mean latency period was 807 days (2.2 years) with an SD of 1461 days (4.0 years) and a range between 'minutes after start' to 23 years. Eight cases had a latency period of $\leq$ 2 months.

The amount of vitamin B_6 in the products ranged from 1.4 to 100 mg per tablet, but intake could be higher than 100 mg because the patient might have taken multiple tablets. For instance, one patient used one tablet of 75 mg and one of 50 mg vitamin B_6. One report considered a liquid dosage form with 0.4 mg vitamin B_6/100 ml. In five products, the amount of vitamin B_6 was not given in milligrams but as a percentage of the recommended daily dose; this varied between 200 and 4000%. In 38 cases, the dosage of vitamin B_6 in the products was equal to or higher than the maximum acceptable daily intake of 25 mg for adults [7], and 22 of these cases had a dosage $\geq$ 50 mg. The dosage was unknown in 27 cases.

The serum level of vitamin B_6 was known in 36 cases. These varied from 88 to 4338 nmol/l. In all but two cases (88 and 145 nmol/l), the reported serum levels were higher than the reference values of 51–183 nmol/l [6]. Mean serum vitamin B_6 level was 907 nmol/l, and the median was 945 nmol/l. Both the dosage and the serum level of vitamin B_6 was known in 29 cases. However, no statistically significant correlation between the serum vitamin B_6 level and the milligrams of vitamin B_6 in the product could be found (Pearson correlation $r = -0.876$, $p = 0.65$).

The highest serum value was reported by a general practitioner from a 63-year-old woman who had used a product with pyridoxine 50 mg daily for 2 years before she developed neuropathy. In two patients, reported serum levels decreased after vitamin B_6 was withdrawn; for example, a female aged 24 years without concomitant medication reported neuropathy following the use of vitamin B_6 75 mg daily. After 2.5 months of use, her vitamin B_6 serum level had increased to $>$ 500 nmol/l. After vitamin B_6 was withdrawn, her serum level decreased to 261 nmol/l after a month and she was recovering from her complaints. In total, 30 positive dechallenges were reported; one rechallenge was reported.

The outcome for the causality score of the individual cases using the Naranjo Probability Scale [20] was 'probable' in eight (9.9%) and 'possible' in 82 cases (91.1%). No cases had a Naranjo score of 'unlikely'.

3.2 Causality of the Cases Series

Using the Bradford Hill criteria [21], we assessed the strength of the association, consistency of the cases, specificity of the association, temporality, dose–response relationship, plausibility of the association, coherence, experiment and analogy (Table 1).

Criteria 1: Strength of Association On 4 July 2017, Vigilyze® included 282 cases for the substance pyridoxine and the SMQ 'peripheral neuropathy'. The SMQ

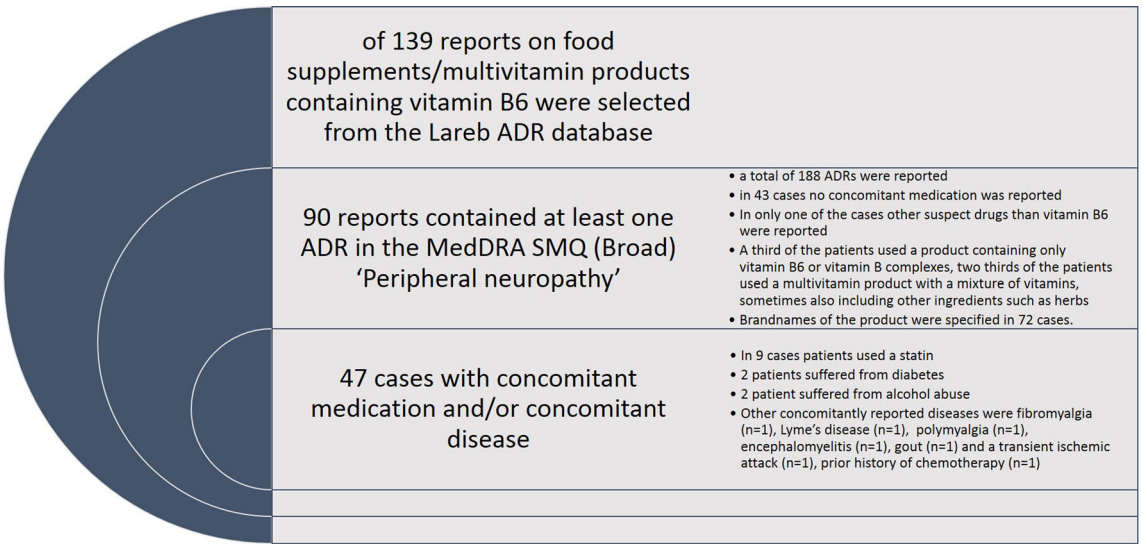

Fig. 1 Description of the selected cases. *ADR* adverse drug reaction, *SMQ* standardized MedDRA query

Table 1 Causality assessment of the case series of vitamin B_6-induced neuropathy using the Bradford Hill criteria

Criteria	Discussion
Strength of association	In the global pharmacovigilance database, Vigilyze®, 282 cases for the substance pyridoxine and SMQ 'peripheral neuropathy' with positive IC_{025} value for hypoesthesia (n = 24; IC_{025} = 1.23), paraesthesia (n = 102; IC_{025} = 0.87), neuropathy peripheral (n = 39; IC_{025} = 0.81), polyneuropathy (n = 7; IC_{025} = 0.68) and muscular weakness (n = 44; IC_{025} = 0.60). This is supportive for an association
Consistency	This case series of Dutch ADR reports is consistent with previous reports from the literature (clinical studies, case series and case reports). The reactions had a similar pattern in clinical features and time to onset. This is supportive for an association. However, reported dosages were sometimes lower than generally described in the literature. No epidemiological studies were found
Specificity	In the 90 reports, a total of 188 ADRs were reported. Mostly these ADRs were nervous system disorders related to neuropathy. Few non-related ADRs were reported. This is supportive for an association. In 43 cases, no concomitant medication was reported. This does not exclude that concomitant use of drugs previously associated with neuropathy can be an alternative explanation. In nine cases, patients used a statin concomitantly, for which neuropathy is a known ADR
Temporality	All reactions manifested after the suspected drug was administered, and time to onset of reactions was usually after a prolonged period, the mean latency period was 807 days (2.2 years) ± SD 1461 days (4.0 years). This is supportive for an association
Biological gradient (dose–response relationship)	Serum vitamin B_6 levels were known in 36 cases and higher than reference values in 34 cases. However, no statistical correlation between dose and vitamin B_6 blood levels was found
Plausibility	A recent study (2017) indicated that the neuropathy observed after taking a relatively high dose of vitamin B_6 supplements is due to pyridoxine. Vrolijk et al. [1] stated that "The inactive vitamer pyridoxine competitively inhibits the active PLP. Consequently, symptoms of vitamin B_6 supplementation are similar to those of vitamin B_6 deficiency." [1] This is supportive for an association
Coherence	The reasoning about cause and effect as present in the aforementioned criteria are in line with each other and supported by the existing knowledge. This supports the existence of a causal relationship
Experiment	30 positive dechallenge cases, one rechallenge, which was positive. This criterion is of limited value as there is almost no information about experiments with rechallenges
Analogy	This criterion is of limited value here as there is no analogous agent to vitamin B_6

ADR adverse drug reaction, *IC_{025}* lower end of a 95% credibility interval for the information component, *SD* standard deviation, *SMQ* standardized MedDRA query

incorporated cases with 22 different MedDRA® PTs. Five PTs had a positive IC_{025} value: hypoesthesia (n = 24; IC_{025} = 1.23), paraesthesia (n = 102; IC_{025} = 0.87), neuropathy peripheral (n = 39; IC_{025} = 0.81), polyneuropathy (n = 7; IC_{025} = 0.68) and muscular weakness (n = 44; IC_{025} = 0.60). As shown in Table 2, associations

with the largest number of reports and generally most specific for chronic neuropathy are disproportionally present, which is supportive of an association.

Criteria 2: Consistency of the Cases Most of the available literature on vitamin B_6 and neuropathy is based on case series, case reports, and (small) clinical studies. A limited number of clinical studies have also been conducted without finding neuropathy related to vitamin B_6 use [25–27]. However, a review of these studies by the Scientific Committee on Food of the European Commission stated that many of these were of insufficient duration, did not assess symptoms sufficiently rigorously to be of value, had a small group size or provided no data on possible pyridoxine neuropathy [28].

This case series of Dutch ADR reports has a pattern in clinical features and time to onset similar to those of published cases. Reported dosages in the literature vary from 24 mg [9] to extremely high dosages of multiple grams used daily [29–31]. In 37 of the reports to Lareb, the vitamin B_6 dosage in the products was equal to or higher than the maximum acceptable intake of 25 mg for adults [8] but generally lower than the mega doses described in the literature (see Table 3). In 25 cases, the dosage per tablet was < 25 mg, but patients might have taken multiple dosage forms.

Table 2 Disproportionality on MedDRA® preferred term level of the cases within the standardized MedDRA query 'peripheral neuropathy' in the global individual case safety reports database Vigibase® (data extraction 4 July 2017)

Reaction (PT)	No. observed	IC_{025}
Hypoesthesia	94	1.23
Paraesthesia	102	0.87
Neuropathy peripheral	39	0.81
Polyneuropathy	7	0.68
Muscular weakness	44	0.60
Peripheral sensory neuropathy	4	− 0.13
Acute polyneuropathy	2	− 0.35
Neuritis	3	− 1.23
Neuralgia	3	− 2.15
Polyneuropathy chronic	1	− 2.24
Burning sensation	6	− 2.40
Sensorimotor disorder	1	− 2.42
Gait disturbance	10	− 2.46
Axonal neuropathy	1	− 2.48
Peripheral sensorimotor neuropathy	1	− 2.53
Hypotonia	3	− 2.91
Areflexia	1	− 3.49
Dysesthesia	1	− 3.88
Sensory loss	1	− 3.97
Muscle atrophy	1	− 4.38
Sensory disturbance	1	− 5.17
Skin burning sensation	1	− 5.30

IC_{025} lower end of a 95% credibility interval for the information component, *PT* MedDRA preferred term

Criteria 3: Specificity Using a broad SMQ is not a very specific method to pinpoint an ADR. In addition, an ADR report can contain multiple ADRs. Many of the cases described neuropathy, peripheral neuropathy, or polyneuropathy without describing all the symptomology, and other cases described neuropathic pain, paresthesia, burning sensations, numbness or tingling of extremities. For instance, "tingling of legs aggravating to muscle weakness of lower limb" and "numbness of extremities (arm and thumb) and neuropathic pain" or "numbness in leg and balance difficulty." Other cases described symptoms in association with an elevation of their vitamin B_6 level: "B_6 increased and burning sensation in the foot and lower leg and numbness of the big toe" and "tingling of extremity (lower legs) and vitamin b_6 increased (three times above the normal level)."

Many patients specified that they were seen by a neurologist, but few diagnostic test results for neuropathy were reported. One patient 45-year-old woman reported neuropathy following 3.5 years of vitamin B_6 use. Electromyogram (EMG), magnetic resonance imaging (MRI), ultrasound, and lumbar puncture showed no abnormalities, but the vitamin B_6 content in her blood was high (> 500 nmol/l). The following symptoms were reported as attributed to the neuropathy: strange feeling in right thigh, sensory disturbance, muscle twitching, involuntary muscle movements in rest, burning pain in both knees and fibula cups, burning pain, mushy feeling buttocks and painful hips after sleep. The patient had recovered almost completely 2.5 years after cessation of the vitamin supplements.

Another woman (aged 74 years) reported small fiber peripheral neuropathy with symptoms: coldness of limbs and tingling of extremity (tingling feet, aching feet, very difficult to walk) following administration of vitamin B_6 with a latency of 4 months after start. EMG was not abnormal, abnormal warm and cold sensation thresholds were suggestive of small-fiber neuropathy according to her neurologist. Vitamin B_6 was withdrawn. The patient was treated with gabapentin, triamcinolone injection and physiotherapy. At the moment of reporting she had not recovered.

One patient experienced a burning sensation all over the body, which meant the case was selected with the SMQ used, but the short latency period and treatment indicates that an allergic reaction was more likely than an acute neuropathy. Concomitant medication was reported in 47 cases, and a relation with some of the concomitantly used drugs such as statins cannot be ruled out.

Table 3 Literature on vitamin B_6-related neuropathy

Study (type of study)	Pt numbers and characteristics	Vitamin B_6 dosage	Duration of use before reaction	Description of neuropathy
Schaumburg et al. [46] (1983) (case series)	Seven healthy adults aged 25–47 y	2–6 g/d	Mo	Ataxia and severe sensory-nervous-system dysfunction. Four were severely disabled; all improved after withdrawal. Nerve biopsies in two pts showed widespread axonal degradation
Dalton [47] (1985) (case series)	58 women with PMS	50–500 mg	–	Reduction of neuropathic complaints 2 mo after stopping vitamin B_6
Foca [31] (1985) (case report)	One 81-y-old woman, indication treatment for carpal tunnel syndrome	Gradually increasing dose to 4.5 g/day	Mo	Nerve conduction studies revealed slowing of motor conduction velocities, prolonged F-wave latencies, prolonged sensory latencies in both lower extremities
Parry and Bredesen [48] (1985) (case series)	16	0.2–5 g/d	Varied	Pure sensory central–peripheral distal axonopathy. Improvement after discontinuation of pyridoxine noted for pts who were followed for longer
De Zeghler et al. [49] (1985) (case report)	One 1-y-old girl	At 9 wk, dose increased from 400 to 1000 mg daily	1 wk	After 1 wk on higher dosage of pyridoxine 1000 mg/d, pt had become areflexic; EEG was abnormal. Pyridoxine blood levels were too high. Recovered after dosage was lowered to 400 mg
Friedman et al. [50] (1986) (case report)	One woman with menstrual water retention syndrome	2 g/d	2 y	Sensory peripheral neuropathy, recovered after discontinuing vitamin B_6
Dalton and Dalton [12] (1987) (case–control study)	172: women with PMS taking vitamin B_6, cases with neurological symptoms, controls without symptoms	<50 to < 500 mg	<6 mo to > 5 y	Raised serum B_6 level in 103 women, 60% of whom had neurological symptoms, which disappeared when B_6 was withdrawn and reappeared in four cases when B_6 was restarted. Mean dose taken by cases and controls was comparable, cases had taken vitamin B_6 for a significantly longer period
Waterston and Gilligan [51] (1987) (case report)	One 20-y-old woman	1000 mg/d for 12 mo	–	Sensory neuropathy, 4 mo after drug cessation marked recovery
Albin et al. [52] (1987) (case report)	Two pts, both treated for mushroom intoxication	Patient 1: 132 g IV over 3 d Patient 2: 183 g IV over 3 d		Both developed an acute, severe and permanent sensory deficit
Santoro et al. [53] (1991) (case report)	One 54-y-old man, treatment for PTB with isoniazid 400 mg/d	600 mg/d	Mo	No recovery 8 mo after withdrawal from isoniazid. However, improvement after discontinuation of pyridoxine. Recovery was slow and still incomplete after 4 y
Berger et al. [54] (1992) (case series)	Five healthy volunteers	Either 1 or 3 g/d	≤7 mo	In all pts, sensory symptoms and QST abnormalities occurred concurrently and were dose related
Morra et al. [30] (1993) (case report)	One 50-y-old woman	10 g/d	5 y	Severe sensory and mild motor neuropathy consisting of loss of touch, temperature, pin-prick, vibration and joint-position in all extremities in a stocking-glove distribution and slight ataxia

Table 3 continued

Study (type of study)	Pt numbers and characteristics	Vitamin B_6 dosage	Duration of use before reaction	Description of neuropathy
de Kruijk and Notermans [9] (2005) (case report)	Two men, 60 and 65 y	24 and 40 mg/d, respectively	Y	One pt with bilateral numbness in hands and leg pain. Serum level 126 nmol/l (reference value: 35–110). Other pt with painful tingling in legs. Serum level > 500 nmol/l (reference value 35–110)
Wyatt et al. [55] (1999) (systemic review of published and unpublished PL-controlled RCTs)	526 women with PMS	50–600 mg	≤4 mo	One case neurological side effects
Scott et al. [10] (case series)	26	20 pts (76.9%) reported daily vitamin use; dosage unknown	Unknown	26 pts with sensory complaints had elevated serum B_6 levels (mean 68.8 ng/ml). 21 pts (80.8%) reported only sensory complaints. Nine of 26 had abnormal EMG/NCS. Eight patients had an abnormal QST
Gdynia et al. [29] (2008) (case report)	One 75-y-old man	9.6 g/d	3 y	Pyridoxine blood level was1850 µg/l (normal 40–120 µg/l). Muscle weakness and motor findings on electrophysiological testing suggested a pure sensory neuronopathy
Kulkantrakorn [11] (2014) (case series)	Three pts aged 80, 83 and 83 y	600 mg/d	3–10 y	Markedly elevated vitamin B_6 blood levels. Electrodiagnostic tests showed symmetric axonal sensory polyneuropathy in two pts. 2 y after vitamin B_6 discontinuation, pts had not recovered
Visser et al. [33] (2014) (case–control study)	381 pts with CIAP vs. 140 healthy controls	Vitamin B_6 use and levels in pts vs. controls	–	Vitamin B_6 levels in pts, daily dose, cumulative dose, duration of supplement use not significantly higher vs. controls. More pts (31%) than controls (22%) used vitamin B_6-containing supplements
Bacharach et al. [56] (2017) (case report)	One 41-y-old woman	B_6 supplement (dosage unknown) and energy drink (B_6 2000% of DRD)	Mo	Pyridoxic acid blood level of 463 mg/l (normal 3–30 mg/l), 2 y of progressive burning pain, numbness, tingling, and weakness in a stocking-glove distribution. EMG/NCS demonstrated chronic sensory polyneuropathy

CIAP chronic idiopathic axonal polyneuropathy, *d* day(s), *EEG* electroencephalogram, *EMG* electromyogram, *IV* intravenous, *mo* month(s), *NCS* nerve Conduction Studies, *PL* placebo, *PMS* premenstrual syndrome, *pt(s)* patient(s), *PTB* pulmonary tuberculosis, *QST* quantitative sensory testing, *RCT* randomized controlled trial, *wk* week(s), *y* year(s)

Criteria 4: Temporality The most common form of neuropathy is axonal degeneration, which occurs over weeks to months after exposure to a suspect drug [32]. Furthermore, in the literature, reported latency periods for drug-induced neuropathy are generally months to years as shown in Table 3. Therefore, cases with a very short latency period ($n = 8$) are not supportive of a causal relation. However, most cases ($n = 82$) had a supportive latency.

Criteria 5: Biological Gradient (Dose–Response Relationship) A dose–response relationship increases the likelihood of a causal relation [22]. However, no statistically significant correlation between the serum vitamin B_6 level and the milligrams of B_6 in the product could be found.

Since some cases reported (very) high serum B_6 levels for low dosages, we cannot exclude that patients took multiple dosages of the product per day or that the declaration of the milligrams on the package of the product was incorrect.

Criteria 6: Plausibility Vrolijk et al. [1] studied the neurotoxicity of the different forms of vitamin B_6 in in vitro models. Cells were exposed to pyridoxine, pyridoxamine, pyridoxal, PLP or PMP for 24 h, after which cell viability was measured. Vrolijk et al. [1] stated that "this study indicated that the neuropathy observed after taking a relatively high dose of vitamin B_6 supplements is due to pyridoxine. The inactive form pyridoxine competitively inhibits the active PLP. Consequently, symptoms of vitamin B_6 supplementation are similar to those of vitamin B_6 deficiency". This plausible mechanism is supportive of an association.

Criteria 7: Coherence Histopathological changes present in cases of neuropathy can be explained by existing theories and are in line with the presence of dose dependency and time to onset of the reaction.

Criteria 8: Experiment Working with spontaneously reported ADRs, we do not have evidence based on randomized experiments. Instead, information, especially on positive rechallenges and, to a lesser extent, positive dechallenges might be viewed as supportive information for this criterion. In total, 30 positive dechallenges were reported. However, since (poly)neuropathy can be irreversible, information on dechallenges is of limited value. In 29 cases, there was no positive dechallenge, meaning the product was withdrawn but patients had not recovered at the time of reporting. In the other cases, information on dechallenge was unknown. Only one rechallenge was performed, which was positive. One patient had used a vitamin B_6 supplement in the past, which led to elevated vitamin B_6 blood levels that recovered after cessation of the product. The second time she used a vitamin B_6 product, her blood levels increased again and this time she experienced numbness and pain in her feet.

Criteria 9: Analogy This criterion is of limited value here, as there is no analogous agent to vitamin B_6.

4 Discussion

4.1 What is Already Known?

Polyneuropathy related to decreased levels of vitamin B_6 is well known. In contrast, the association between elevated levels of pyridoxine and neuropathy is less known [10]. Vrolijk et al. [1] stated that, "remarkably, sensory neuropathy is seen in vitamin B_6 toxicity as well as vitamin B deficiency." The toxic effects of pyridoxine depend on both the dose and the duration of intake [13].

Several case series have described neuropathy as an effect of elevated vitamin B_6 levels, albeit with extremely high doses of vitamin B_6 in some cases. However, literature also exists on prolonged use of vitamin B_6 in patients who did not develop neuropathy [26]. Evidence is largely based on case reports, case series and clinical studies, as seen in Table 3, all with their own limitations. Larger epidemiological studies are lacking. One case–control study published in 2014 [33] investigated vitamin B use in patients with chronic idiopathic axonal polyneuropathy (CIAP) versus healthy controls. On the basis of this study, an association between CIAP and vitamin B_6 exposure or elevated vitamin B_6 levels appeared unlikely. However, most reports from the literature concern patients with a (severe) sensory ataxic neuropathy, which is quite different from the phenotype seen in CIAP, where sensory ataxia is not a prominent feature [33]. As with all adverse reactions, the dosage and timing at which patients are prone to develop adverse reactions is subject to a patient's individual susceptibility.

4.2 What Does this Study Add?

This study adds a large case-series of 90 reports to the existing evidence on vitamin B_6-induced neuropathy and an extensive review of the literature on this topic.

Causality assessment in pharmacovigilance is challenging. But, as Edwards has recently said, "The fullest assessment of clinical cases still gives critical information useful to clinicians" [34]. For this article, we conducted a causality assessment of the case series of 90 spontaneously reported cases of vitamin B_6-induced neuropathy. All cases were individually assessed by trained assessors, and we included the score on the Naranjo algorithm [20] and an assessment according to the Bradford Hill criteria [21]. The Naranjo algorithm is still the most widely used causality methods, although its performance in capturing the causal relation for all types of spontaneous ADRs is debatable [35–37]. We found the Bradford Hill criteria [21] to be a valuable tool in this assessment, but we made some adjustments to the original criteria he proposed. Because an incidence or risk for this association was not available, an indicator value for disproportionate reporting was used to get an impression about the strength of this association among the reported cases in Vigibase®. Indeed, this IC value and related measures of disproportionality are used by the UMC and other pharmacovigilance centers merely for statistical signal detection [23, 24]. Like any other value of disproportionality, the IC informs the strength of the association in the dataset under study. Of course, this does not necessarily imply a causal relationship in the population of those using the drug, but it may be indicative for one [38]. It goes without saying that other supportive

information is needed for the assessment of causality. Russom et al. [39] used a similar approach in the assessment of a case series.

We could not fully assess all the Hill criteria for this case series. However, Bradford Hill [21] stated,

"None of these nine viewpoints can bring indisputable evidence for or against a cause and effect hypothesis …. What they can do, with greater or less strength, is to help answer the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

The information throughout the cases is generally consistent, and many cases included laboratory values. More than 75% of the reports were made by patients themselves, showing their value as reporters of useful drug safety information.

In 36 cases, the serum level of vitamin B_6 was known. These varied from 88 to 4338 nmol/l and was above reference values in 34 cases. Interestingly, Lareb has received reports of neuropathy even at relatively low dosages of vitamin B_6. In 38 cases, the dosage of vitamin B_6 in the products was equal to or higher than the maximum acceptable intake of 25 mg for adults [8], and 22 of these cases had a dosage $\geq$ 50 mg.

The study by Vrolijk et al. [1] indicated that the toxicity of vitamin B_6 is determined not only by the dose but also by the vitamer in which it is taken. They suggested that "perhaps it might be better to replace pyridoxine by pyridoxal-5′-phosphate or PLP as vitamin B_6 supplements, which are much less toxic. In this way, the vitamin B_6 paradox may potentially be prevented."

4.3 Maximum Safe Daily Dose

When determining the maximum safe daily dose of vitamin B_6, the total intake per day is used, thus dietary intake and any intake via supplements. There is a large margin between the European Food Safety Authority (EFSA)-established safe upper limit of vitamin B_6 25 mg per day and the intake of B_6 through the diet [8, 40]. In a Dutch National Food Consumption survey, the median vitamin B_6 intake from foods ranged from 1.4 to 2.2 mg/day for men and from 1.3 to 1.8 mg/day for women. Accounting for vitamin B intake from dietary supplements increased this by 5–17% at the median (1.5–2.4 mg/day for men and 1.4–2.1 mg/day for women for total vitamin B_6 intake) [2]. About 1% of Dutch women exceed the safe upper limit by using vitamin supplements [2]. Food supplements, including vitamins, are used by a large number of people. Because dietary supplements are sold over the counter without a prescription, consumers may incorrectly assume they carry no risk [41]. Although many manufacturers of food supplements adhere to the recommended safe upper limit of pyridoxine 25 mg, Lareb's reports show that a fair amount of products on the Dutch market also exceed this upper limit. Lareb's reports were used in an advice to the Dutch Minister of Health that the maximum allowed dosage of vitamin B_6 in supplements should be set at 21 mg [42]. The Dutch Minister of Health agreed in December 2016 that this advised maximum allowed dosage of vitamin B_6 will be laid down in a law [43].

4.4 Limitations of the Study

Our main limitation is that we were not able to check whether the amount of vitamin B_6 declared on the product's packaging was the actual amount in the product or whether the patient took more than the advised dosage on the package and did not declare this in their ADR report. This could be the reason that no correlation was found between the milligrams of vitamin B_6 used and the reported vitamin B_6 serum levels. We also do not have information on the exact composition of the products, considering which vitamers are present.

However, it is also possible that, for some patients, the use of vitamin B_6 was not the (main) cause of the reported neuropathic complaints. The causes for developing peripheral neuropathy are myriad; Bernstein [44] stated that prior susceptibility might be a reason why some patients develop neuropathies relating to vitamin B_6 while others do not. Pre-disposing factors might consist of family histories and drug, alcohol and nutritional status [44]. Many reports of peripheral neuropathy were patient-reported and—although many contained information on vitamin B_6 blood levels—were not supported by a physician's assessment or electrodiagnostic data. During the case-by-case assessment of the reports, follow-up was requested in many cases, but these are mainly patient's reports, so we do not have detailed data on clinical examinations. Our center does not routinely ask for medical confirmation of reports received from patients [45]. In 36 of the 90 reports of peripheral neuropathy in patients receiving vitamin B_6, the B_6 serum level was known. It is possible that patients developed a peripheral neuropathy such as CIAP coincidentally. We have no information from the cases that any of the patients had vitamin deficiency, but we cannot be sure of this. In two cases, alcoholism was reported, and vitamin B deficiency is a known problem with this condition [44]. Similarly, we only know the dosage of B_6 in 37 cases, for the others, whether patients may or may not have been taking the recommended daily dose is unknown.

Unfortunately, it is not possible to relate the number of cases to the number of users in the Netherlands. No comprehensive data are available on sales of these products,

including web sales from a multitude of vendors. Based on our reports, we are unable to assess the magnitude of the actual risk of the adverse effects at the dose considered the maximal acceptable intake.

5 Conclusion

Causality assessment of a case series of 90 reports to Lareb indicates it is plausible that vitamin B_6 supplements may cause complaints such as neuropathies. This is especially so with higher dosages and prolonged use, as is also known from the literature, but causality cannot be excluded for dosages < 50 mg/day. Because high-dosage vitamin B_6 supplements are readily available for consumers, it is important consumers are made aware of the possible risks associated with the use of these products.

Compliance with ethical standards

Conflict of interest Florence van Hunsel, Sonja van de Koppel, Eugène van Puijenbroek and Agnes Kant have no conflicts of interest.

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