Indices of Pyridoxine Levels on Symptoms Associated with Toxicity: A Retrospective Study

Aliya N. Chaudary;[1] Adam Porter-Blake;[2] Patrick Holford[2]

Abstract

Background: The UK Expert group for Vitamins and Minerals have suggested that ingestion of more than 10 mg vitamin B_6 for an extended period might cause sensory peripheral neuropathy. So far few studies have been performed on individuals who have taken large doses of this vitamin for any length of time.

Objective: To evaluate the safety of vitamin B_6 supplementation when given in daily doses greater than 30 mg over three months. To suggest a suitable safe upper level for vitamin B_6 according to LOAEL (low observable adverse effect level) and NOAEL (no observable adverse effect level).

Methods: A retrospective cohort study was conducted in which data on symptoms associated with vitamin B_6 toxicity (tingling hands, insomnia, rashes and acne) were obtained from 555 clients aged between 14-76 years. Clients who attended a nutritional therapy practice and were given above 30 mg of supplemental vitamin B_6 for over 3 months were targeted. Client characteristics, symptoms, vitamin B_6 dose and duration were collected from completed Nutrition Programme Questionnaires used by Nutritional Therapists from The Institute for Optimum Nutrition. A t-test, assuming equal variances, was used to evaluate the association of dose range and duration with symptoms associated with toxicity.

Results: Statistically significant improvements ($p<0.001$) in all the symptoms were evident for participants taking the dose range between 30–230 mg of vitamin B_6, as opposed to further toxicity. The most improvements were observed in symptoms of insomnia. Participants who took 101–150 mg/day experienced the most improvements ($p<0.05$) in the symptoms related to B_6 toxicity. 147 participants experienced tingling hands before B_6 supplementation. 71.4% of these participants experienced improvements in tingling hands. 38.1% (largest portion) of these participants were taking 101–150 mg/day of vitamin B_6.

Conclusions: There appeared to be no association between symptoms associated with vitamin B_6 toxicity and vitamin B_6 dose (between 30mg and 230mg) during a period of 3–27 months. A suitable vitamin B_6 NOAEL of 100 mg / day and a suitable LOAEL of 150 mg / day is suggested.

Keywords: Vitamin B_6, toxicity, tingling hands, dose, safe upper levels.

Introduction

Vitamin B_6 has been subjected to much debate by many scientists who have different views about the safe levels of administering vitamin B_6 in supplemental form. Vitamin B_6 is a water-soluble vitamin existing in three natural forms including pyridoxine (or pyridoxol, the alcohol), pyridoxamine (the amine) and pyridoxal (the aldehyde). All three forms undergo phosphorylation in the 5-position by pyridoxine kinase. Oxidation of the intermediate compounds follows to form the active coenzyme pyridoxal-5-phosphate (PLP). Pyridoxal is directly phosphorylated to PLP whereas pyridoxine and pyridoxamine are first phosphorylated to their counterparts pyridoxine phosphate and pyridoxamine phosphate and then converted to PLP by pyridoxal phosphate oxidase.[1,2] Pyridoxine hydrochloride is the synthetic pharmaceutical form.[3] This vitamin is a coenzyme for several hundred biochemical reactions and metabolic pathways such as protein and lipid metabolism as well as hormonal metabolism,

1.Corresponding author, E-mail: aliya.chaudary@ion.ac.uk
2.Institute for Optimum Nutrition, Blades Court, Deodar Road, London SW15 2NU

immune function and neurotransmitter synthesis. Vitamin B_6 is bio-available once it is converted to PLP. This requires good levels of co-factors such as magnesium and riboflavin (vitamin B_2).[4] Magnesium is required for the phosphorylation of all the forms of vitamin B_6 by pyridoxal kinase as the Mg2+ ATP complex. Riboflavin is required for the conversion of pyridoxine phosphate (phosphorylated form of pyridoxine – inactive) which will go on to form PLP.[1]

Vitamin B_6 is widely distributed in low concentrations in all animal and plant tissues, but particularly in meats, organ meats, brewers yeast, bananas, walnuts, carrots, and wheat germ. The availability of pyridoxine from different foods is variable. Absorption of the vitamin from dietary sources is only 60–80% from the pure vitamin.[5] Vitamin B_6 is also very vulnerable and is easily lost in food processing. One such method is canning as pyridoxal and pyridoxamine are sensitive to oxidation during heat treatments. Milling and refining of grains causes loss of almost all the original vitamin B_6. Even freezing and thawing may cause considerable loss of the vitamin.[6]

Requirements for vitamin B_6 are worked out in relationship to the metabolism of amino acid, tryptophan. In the UK it is set in the region of 15 micrograms per gram of dietary protein. According to these calculations, RNI (recommended nutrient intake) is approximately 1.4 mg and 1.2 mg per day for males and females respectively.[7] Requirements for vitamin B_6 is increased by ingestion of alcohol, coffee, oral contraceptives, antibiotics, and the food colouring tartrazine. Other factors, which reduce B_6 levels, are smoking, radiation, air pollution and a high protein intake. A daily supply is needed as surplus is excreted in the urine within eight hours after ingestion, and is not stored in the liver, but found exclusively in the muscles.[8] Biochemical evidence of inadequate B_6 status has been found in 10-25% of the UK population.[9]

Vitamin B_6 is one of the few water-soluble vitamins associated with some toxicity. Symptoms of toxicity associated with vitamin B_6, as outlined by the Expert Group on Vitamins and Minerals (EVM) in their consultation document, are referred to as tingling hands and feet, a stumbling gait, perioral numbness, sensory loss, lack of muscle coordination, night restlessness (Insomnia), vivid dreams, sun sensitivity, and an acne - like rash.[10] The main indication of pyridoxine toxicity has been the peripheral or sensory neuropathy.

Sensory neuropathy was reported in seven adults consuming 2000–6000 mg daily of pyridoxine over periods of 2–14 months. Although there was residual damage in some patients, withdrawal of these high doses resulted in a considerable recovery of sensory nerve function.[11] Leklem reported that neuropathy was evident at doses greater than 1000 mg per day. He also proved with a few case reports of individuals developing neuropathy at doses less than 500 mg daily.[12] However he noted that none of the studies, in which an objective neurological examination was performed, found evidence of sensory nerve damage at pyridoxine intakes less than 200 mg per day. These levels were also related by another report.[13]

Cohen and Bendich in 1986 conducted a literature review on the adverse effects associated with the administration of high oral doses of pyridoxine to animals and man. In the human data, doses greater than 500 mg per day for a prolonged period caused sensory nerve damage. However, doses less than 500 mg per day appeared to be safe if administered between six months and six years. Although, evidence between 500–1000 mg were not compelling at the time they considered doses greater than 500 mg per day to be potentially neurotoxic.[14] Other studies have also reported that doses greater than 500 mg per day have shown neurological damage.[9,15] In addition to this, Bender in 1989 also concluded that

even modest pyridoxine doses of 50–100 mg per day were potentially hazardous.[9]

The lowest level that has been reported in a clinical study to cause neurological damage in humans was 10 mg per day. This study conducted by Dalton and Dalton,[16] has been extensively criticised and even discredited by many in the medical field. Regardless of this, the study has been regularly used as reliable evidence for recommending a low dose of vitamin B_6 in supplements and food for the UK population. In response to this, the editor of the prestigious medical journal Lancet, commented that "the UK COT (Committee on Toxicity in Foods, Consumers Products and the Environment) seem to have based their vitamin B_6 of 10 mg recommendation on the slimmest of evidence."[17] Many studies and literature reviews have portrayed their disapproval of the Dalton study.[18-23] Chalmers and Barker concluded that the Dalton study is fatally flawed due to limited data and missing evidence, listing a number of missing evidence that were not accounted for.[24] Austin highlights that most symptoms reported in the Dalton trial such as bone pain, shooting chest pains and many others, are not part of the consistent picture of the vitamin B_6 toxicity reported by other researchers.[25] He explains that what the patients in the Dalton study were suffering from was not vitamin B_6 toxicity. Becketts points out the poor design, inadequate documentation, unfounding symptoms related to vitamin B_6 toxicity and the inconsistencies in the results.[26] It is interesting to note that in the Dalton Study - Table 1, as the daily dosage increases from 50 mg to 100 mg the percentage of women with neurological symptoms also increases. However, as the daily dose increases from 100 to 500 mg the percentage of women with neurological symptoms decreases. From this table, no association between higher daily doses of vitamin B_6 and neurological symptoms is apparent. Yet the authors conclude otherwise.

Much evidence has shown that pyridoxine doses above 10 mg per day are safe. A literature review conducted in 1978 by Haskell revealed no incidence of adverse effects in patients treated with daily doses of 20–100 mg for a period of 3 to 4 years.[27] More recent studies have shown that doses of 100 mg or less is safe to avoid any risk of neuropathy.[18,28-31] Furthermore, studies involving large population groups with carpal tunnel syndrome, all adults using 100-150 mg per day showed minimal or no toxicity, especially in five to ten year studies.[32]

Ellis and McCully have presented suggestive evidence that cardiovascular events may be prevented or postponed in patients using high dose supplemental pyridoxine on a long-term basis.[33] Ellis recommended 100–300 mg of supplemental pyridoxine per day and claimed that they were well tolerated in adults. He observed that high dose pyridoxine can alleviate pregnancy-induced oedema as well as carpal tunnel syndrome precipitated by pregnancy and it was standard for him to prescribe 200–300 mg per day.[34]

Many studies provided evidence to suggest that the upper safe level of pyridoxine administration should be 200 mg.[12,13,15,22,35-38] Likewise, some studies even suggest that 200 mg per day is safe enough to be a no observable adverse effect level (NOAEL).[23,38,39] NOAEL is the level which is safe enough that no observable adverse effect has been seen at this dose when taken over long periods of time. According to the Institute of Medicine, NOAEL is a dosage level which "requires no application of a safety factor to determine a safe intake, based on the most sensitive subgroup." These same studies have also provided a low observable adverse effect level (LOAEL) of 500 mg per day. LOAEL is the dose where toxicity has rarely occurred, and then only for some people with unusual sensitivities, who are considered to be in sensitivities subgroups.[39] This upper safe level has also been supported by other studies.[14,40] which were suggested under the impression

that clinical neuropathy at this level is rare but if it were to occur that it is reversible once it is discontinued promptly.

Sensory neuropathy could be caused by a loss of action potential and slowed conduction in sensory Na+-channels brought about by the malfunction of ganglioside. It is proposed that PLP deficiency disrupts the synthesis of ganglioside.[1,41] Another mechanism, which may have caused vitamin B_6 toxicity, has been suggested. Helen Fullerton proposed that aldosterone, a metabolite of progesterone that induces a diuretic loss of riboflavin and magnesium, caused an underactivation of enzymes dependent on flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD) and magnesium. This in turn, induced an accumulation of circulatory pyridoxal. This increase in pyridoxal propagated a down-regulation of pyridoxal kinase mRNA, thus restricting the amount of PLP via this pathway. The combined deficiencies of PLP, magnesium and riboflavin may have caused the sensory neuropathy. However, the alternative route from pyridoxine and pyridoxine phosphate allowed the synthesis of PLP via the FMN- pyridoxine phosphate oxidase pathway. It is proposed that tissues of peripheral sensory nervous system do not contain pyridoxine phosphate oxidase.[1] Symptoms associated with vitamin B_6 toxicity, in particular neurotoxicity, is also believed to be due to exceeding the liver's ability to phosphorylate pyridoxine to PLP. The resulting high pyridoxine blood levels could directly lead to neurotoxicity or it may compete for the binding sites with PLP.[41] Consequently, this causes a relative deficiency in this active metabolite.[1,35,42] Thus, the symptoms of vitamin B_6 toxicity can also manifest itself in symptoms very similar to those of deficiency (by which pyridoxine overdose leads to PLP deficiency). Some of these mechanisms were also hypothesised in 1964 by Snell.[43]

Hass has suggested that to lessen the concern of neuropathy-induced by vitamin B_6 toxicity, supplementation can be given in the form of PLP especially for doses greater than 200 mg.[35] This is also supported by other authors.[1,44] Moreover, Hass suggests increasing the amounts of magnesium with higher levels of vitamin B_6 to reduce the occurrence of peripheral neuropathy.

The purpose of this study is to establish whether subjects taking daily doses above 30 mg of vitamin B_6 for over 3 months experienced any symptoms associated with toxicity. To determine what degree of symptoms associated with toxicity was apparent from a range of vitamin B_6 dose levels, coupled with dose duration. Finally, to suggest a suitable safe upper level for vitamin B_6.

Methods

Study design and population: The investigation is based on a retrospective cohort of men and women aged between 14 to 76 years who had opted to attend a nutritional therapy practice in the UK for help with a variety of complaints. Nutritional Therapists who graduated from the Institute for Optimum Nutrition were asked to submit forms from those clients who were given above 30 mg of supplemental vitamin B_6 per day for over 3 months. Dietary vitamin B_6 intake was not included and not used in this study. All clients had previously completed a Nutrition Programme Questionnaire (NPQ) which is used to assess their nutritional status and determine the nutritional intervention necessary for the individual concerned. The NPQ consists of four pages, each page asking for specific health-related information. In this study only the first two pages were required. The first page contains the client's personal details, their major health problems and family medical history. The second page is the symptoms analysis page displaying a list of symptoms which are associated with early deficiency signs of specific vitamins and minerals. Clients underlined symptoms on this page from which they felt they suffered regardless of the reason for attending the clinic.

After a number of months ranging from 3 to 42, the clients were asked to complete the relevant parts of the same questionnaire again underlining the symptoms from which they still suffered. The NPQs were then returned to the nutritional therapists who collated the initial NPQ and last NPQ of each relevant client and mailed it to the researchers involved in the study.

In order to operationalize the concept of potential B_6 toxicity, especially 'nerve damage', the symptoms taken from the NPQ which most resembled the early warning signs of toxicity described previously were: tingling hands, insomnia (night restlessness), acne and skin rashes.

Data collection: A total of 584 NPQ's were received, 21 of them were disregarded as they were incomplete, 8 participants were outliers (i.e. outside the range of 3–42 months or 30–250 mg) so were also disregarded, thus 555 NPQ's were used. Each client was allocated an identification number. Gender, age (years), weight (kg), height (metres), body mass index (kg/m2) calculated, major health problem, the initial specified symptoms associated with toxicity and initial dose prescribed were extrapolated from the first NPQ. Follow-up symptoms, total duration (calculated in months) and end dose was collected from the second NPQ. The mean dose was calculated from the start dose and the end dose. The data was tabulated in Word Excel.

Statistical methods and analysis: A simple t-test assuming equal variances was used to analyse the data by statistical means. The data was analysed according to total population and total symptoms then total population and individual symptoms. This information was then matched for dose range and duration of vitamin B_6. For this to be accomplished the population was categorised into dose and duration groups. The subjects were first sectioned into dose categories in 50 mg intervals, for example 0–50 mg, 51–100 mg, 101–150 mg and so on. After this, they were further divided within these groups into duration categories with 3-month intervals. This categorisation further refined the groups so that a dose and duration of vitamin B_6 can be determined and assist in establishing a no observable adverse effect level (NOAEL) and low observable adverse effect level (LOAEL).

Results

Overall symptoms associated with pyridoxine toxicity i.e. tingling hands, insomnia, rash and acne, demonstrated statistically significant ($p<0.001$) reduction in the frequency of the symptoms after vitamin B_6 supplementation during 3–42 months. Thus, improvements in the symptoms were evident over the full dose range of 30–230 mg. When individual symptoms were analysed against the dosage spectrum of 30–230 mg each symptom also demonstrated statistically significant improvements ($p<0.005$). The most improvements were noted in symptoms of insomnia.

Table 1 (pp. 70-71) shows the distribution of the number of symptoms experienced before and after vitamin B_6 supplementation by dosage and duration. The dose range of 101–150 mg showed the most improvements in symptoms associated with toxicity with many statistical significant differences ($p<0.05$) in the symptoms between the duration of 3–27 months. A t-test could not be conducted for Group's 3j to 3n due to the small sample size. Significant improvements were also apparent in the Group 4 who took a dose range of 151–200 mg. However, the improvements were to a lesser extent than shown in Group 3. In the highest dose range of 201–250 mg improvements were noted but were not statistically significant.

Table 2 (p. 72) concentrates on the most common symptom associated with pyridoxine toxicity which is tingling hands (a sign of sensory neuropathy). Supplementation of vitamin B_6 did not aggravate symptoms of tingling hands. In the con-

Table 1. Relations between the numbers of symptoms experienced before and after vitamin B_6 supplementation by daily dose and duration.

group	daily dose (mg)	duration (months)	number of subjects in group	symptoms in group before B_6 (a)	symptom remaining after B_6 (b)	symptom differences (b – a)*
1a	0 - 50	0 - 3	1	1	0	-1
1b		3.1 - 6	5	7	5	-2
1c		6.1 - 9	7	7	2	-5
1d		9.1 - 12	2	0	0	0
1e		12.1 - 15	2	4	0	-4
1f		15.1 - 18	3	0	1	1
1g		18.1 - 21	2	2	0	-2
1h		21.1 - 24	1	0	0	0
1i		24.1 - 27	2	1	0	-1
1j		27.1 - 30	0	-	-	-
1k		30.1 - 33	0	-	-	-
1l		33.1 - 36	1	1	1	0
1m		36.1 - 39	0	-	-	-
1n		39.1 - 42	0	-	-	-
2a	51 - 100	0 - 3	6	7	4	-3
2b		3.1 - 6	40	41	27	-14
2c		6.1 - 9	29	26	16	-10
2d		9.1 - 12	16	13	7	-6
2e		12.1 - 15	5	7	2	-5
2f		15.1 - 18	5	2	3	1
2g		18.1 - 21	4	6	3	-3
2h		21.1 - 24	4	7	1	-6
2i		24.1 - 27	3	3	2	-1
2j		27.1 - 30	4	6	1	-5
2k		30.1 - 33	1	0	1	1
2l		33.1 - 36	0	-	-	-
2m		36.1 - 39	1	1	1	0
2n		39.1 - 42	0	-	-	-
3a	101 - 150	0 - 3	3	6	1	-5
3b		3.1 - 6	53	70	32	-38
3c		6.1 - 9	40	59	19	-40
3d		9.1 - 12	22	34	13	-21
3e		12.1 - 15	13	18	13	-5
3f		15.1 - 18	17	27	6	-21
3g		18.1 - 21	5	11	3	-8
3h		21.1 - 24	14	22	9	-13
3i		24.1 - 27	10	13	3	-10
3j		27.1 - 30	5	3	4	1
3k		30.1 - 33	4	6	4	-2

Table 1 continued. Relations between the numbers of symptoms experienced before and after vitamin B_6 supplementation by daily dose and duration.

group	daily dose (mg)	duration (months)	number of subjects in group	symptoms in group before B_6 (a)	symptom remaining after B_6 (b)	symptom differences (b – a)*
3l		33.1 - 36	0	-	-	-
3m		36.1 - 39	3	1	0	-1
3n		39.1 - 42	0	-	-	-
4a	151 - 200	0 - 3	4	10	8	-2
4b		3.1 - 6	36	58	30	-28
4c		6.1 - 9	20	29	27	-2
4d		9.1 - 12	16	30	14	-16
4e		12.1 - 15	7	16	8	-8
4f		15.1 - 18	6	13	7	-6
4g		18.1 - 21	7	17	9	-8
4h		21.1 - 24	1	2	2	0
4i		24.1 - 27	2	0	2	2
4j		27.1 - 30	3	7	5	-2
4k		30.1 - 33	5	9	7	-2
4l		33.1 - 36	0	-	-	-
4m		36.1 - 39	0	-	-	-
4n		39.1 - 42	0	-	-	-
5a	201 - 250	0 - 3	1	2	2	0
5b		3.1 - 6	52	83	63	-20
5c		6.1 - 9	16	35	27	-8
5d		9.1 - 12	19	33	34	1
5e		12.1 - 15	3	9	1	-8
5f		15.1 - 18	6	10	5	-5
5g		18.1 - 21	4	8	6	-2
5h		21.1 - 24	9	20	11	-9
5i		24.1 - 27	3	9	7	-2
5j		27.1 - 30	0	-	-	-
5k		30.1 - 33	1	3	3	0
5l		33.1 - 36	0	-	-	-
5m		36.1 - 39	0	-	-	-
5n		39.1 - 42	1	3	3	0

• Negative value indicates improvements in symptoms and positive value indicates worsening in symptoms associated with B_6 toxicity.

Table 2. Percentage of participants who experienced no change in the tingling hands symptom or experienced improvement after B_6 was given.

no change in tingling hands

dose (mg)	number of subjects	percentage in group (%)
0 – 50	2	4.8
51 – 100	4	9.5
101 – 150	5	11.9
151 – 200	16	38.1
201 – 250	15	35.7
n	42	100

improvement in tingling hands

dose (mg)	number of subjects	percentage in group (%)
0 – 50	4	3.8
51 – 100	15	14.3
101 – 150	40	38.1
151 – 200	25	23.8
201 – 250	21	20
n	105	100

Total number in both groups = 147

Table 3. Relation between the number of symptoms experienced after vitamin B_6 supplementation and the percentage of participants in the "no symptoms before B_6" group.

number of symptoms after B_6	number of subjects in group	percentage in in group (%)
0	91	80
1	19	17
2	4	3
n	114	100

Table 4. Cumulative amounts of B_6 supplement form matched for dose.

supplement form	cumulative value•	percentage (%)
pyridoxine	5622	93.3
PLP	377.5	6.3
pyridoxine Hydrochloride	27.5	0.4
n	6027	100

•number of tablets x dosage factor

trary, improvements in tingling hands were experienced whereby 105 (71.4%) participants felt the tingling hands had disappeared. The largest percentage of participants to have experienced this were those taking 101–150 mg of vitamin B_6 (38.1%) with 11.9% experiencing no change in the symptom. Furthermore, 38.1 % of participants in the 151–200 mg dose range group felt the tingling hands still remained but 23.8 % of participants in the same dose range experienced improvements.

Discussion

Supplementation of vitamin B_6 greater than 30 mg does not cause toxicity symptoms related to an overdose in vitamin B_6. In fact, improvements in the symptoms were seen. The daily dose that demonstrated the most improvements was between 101–150 mg especially when taken between 3.1–27 months. This duration may have extended for the full 42 months if more participants were included in the longer duration groups. However, this hypothesis cannot be assumed. There is evidence to support the findings seen in this study from previous studies such as the work by Bernstein in 1990 when he confirmed that 100–150 mg per day showed minimal or no toxicity in 5–10 year studies. The dose between 151–200 mg per day also showed improvements particularly between 3.1–21 months of supplementation. However, the same situation applies here for the longer duration groups taking 151–200 mg per day; more participants were needed.

Tingling hands is the most distinct symptom of vitamin B_6 overdose. Out of all the participants in the study 147 (26.5%) experienced tingling hands before supplementation. An improvement in this particular symptom was apparent in 71.4%. The remaining 28.6% of participants noticed no change in the symptom. The majority of the participants (38.1%) who noticed improvements in the symptom were taking 101–150 mg per day. The daily dose of 151–200 mg was a close second with 23.8% participants noticing improvements.

It is important to highlight the possible reasons for having tingling hands before vitamin B_6 was supplemented. Some of the health complaints the participants presented with at the nutrition therapy clinic indicated vitamin B_6 depletion. On analysis the majority of the participants in both the 'no change in tingling hands' group and 'improvements in tingling hands' group had complained about fatigue or ME. Vitamin B_6 has been reported to be deficient in some people with chronic fatigue syndrome.[45] The tingling hands may be early signs of multiple sclerosis. Although participants did not record this as a health problem it may be undiagnosed. The clients may have had these symptoms related to vitamin B_6 toxicity from previous treatments or it could be representing pyridoxine/PLP deficiency.

Although it is apparent that symptoms of tingling hands was reported by a number of participants, it can not be concluded that this was a symptom of B_6 toxicity but may be indicative of underlying pathology which could not be identified from the data available. No conclusion could also be drawn for all dose ranges taken for longer than 27 months due to small sample sizes in these groups.

From the 555 participants 114 of them attended the nutrition therapy clinic with no symptoms associated with B_6 toxicity. Of these participants 91 did not develop any symptoms associated with toxicity. However, the other 23 participants experienced symptoms after vitamin B_6 was given. Of them 19 gained one symptom and the remaining 4 gained two symptoms (see Table 3, p. 72). The majority of the participants in both these categories experienced insomnia. Conversely, all participants in the study with insomnia experienced overall improvement which was statistically significant (see Results). The dose range to have the most affect on these 23 partici-

pants was investigated and was shown to be between 101–150 mg. Again, from the overall findings this dose range proved to significantly improve symptoms of B_6 toxicity. The duration of 3.1–6 months had the most impact on symptoms development as opposed to the longer periods. This could account for the large number of participants in the 'b' groups.

Although this shows that symptoms associated with B_6 toxicity developed in some participants it was demonstrated in 4% of the total sample population. Thus, showing low levels of toxicity. The improvements noted previously have shown statistical significance which outweighs these recent findings. Nevertheless, it can not be overlooked and can be used to verify that high levels of vitamin B_6 does indeed cause symptoms of toxicity that has been observed by other studies.

The question is, if the participants had symptoms associated with toxicity before supplementation of vitamin B_6, worsening of the symptom is expected once B_6 supplementation started. How is it then that improvements are seen in this study? There are three possible explanations.

Firstly, it could have been due to the form or preparation of vitamin B_6 taken by the participants. As Hass and other authors suggested, the concerns for B_6 toxicity may be lessened by giving vitamin B_6 in the active form of PLP if using doses greater than 200 mg per day.[35] The reason for this was that symptoms of PLP deficiency may be masked by symptoms of pyridoxine toxicity. Some of the symptoms of pyridoxine or PLP deficiency are muscle weakness, nervousness, irritability, confusion, insomnia, neuritis and dermatitis;[35] some of which are similar to pyridoxine toxicity. When the preparations of the supplements used in this study were investigated it was found that 93.3% were prepared as pyridoxine, 6.3% as PLP and 0.4% as pyridoxine hydrochloride (see Table 4, p. 72). From this it would seem that the participants may have been deficient in pyridoxine rather than toxic, hence not enough pyridoxine to convert to PLP. Thence, when doses below 200 mg were given, improvements in the symptoms were seen.

The use of PLP as a supplement instead of pyridoxine should not be ignored and should be further investigated. The evidence supporting its use provides a good reason to explore deeper.

Secondly, as well as the health complaints the nutritional therapists assess the clients according to their specific lifestyles. This analysis is incorporated in the NPQ. Certain lifestyles lead to glucose intolerance, stress, low physical activity, low immune function, increased cardiovascular risk; the client may be pregnant or breast feeding, suffering from PMT or is between 14–16 years old. All of these increase the requirements for vitamin B_6. Certain pharmaceutical drugs that are taken can also deplete levels of vitamin B_6 such as oral contraceptives, penicillamine and oral corticosteroids. Hence, although some symptoms relate to B_6 toxicity, the health complaints and lifestyle factors may show that the clients are not receiving enough vitamin B_6. Thence, the use of vitamin B_6 supplements which marked improvements in the symptoms.

The final explanation is that vitamin B_6 may not have been the only supplements that the participants took on a regular basis. They may have been given other nutritional supplements in addition to a dietary regime. Thus, improvements in the symptoms may have occurred due to a combination of diet and supplementation as a whole. As co-factors such as magnesium, zinc and other B vitamins are required in order to metabolise pyridoxine properly, the improved diet and these nutrients including vitamin B_6 (in diet and supplements) could have contributed to the alleviation of the symptoms associated with B_6 overdose.

This study was conducted using a large sample size of 555 participants taking high

dose vitamin B_6 supplements for up to three and a half years. There have been very few studies of vitamin B_6 intake using a sample this large. However, limitations in this study are imminent. This study was undertaken in a retrospective design and not as a controlled trial. This meant that the sample group could not be analysed against a control or placebo group. Thus, the link between vitamin B_6 intake and symptoms associated with toxicity could not be firmly established.

The participants selected for the study are not representative of the general population. It is an opportunity sample and not achieved by random selection. The sample included many individuals who were suffering from specific complaints such as chronic fatigue syndrome and candidiasis, which motivated them to consult a nutritional therapist. These participants may be more likely to report a higher number of perceived adverse symptoms, thus exaggeration is probable. The symptoms which were recalled and recorded in the study, were perceived by the participants, thus owing to another limitation.

Some clients may not have requested a follow-up consultation because they felt their health complaints including symptoms associated with B_6 toxicity were completely treated. As no follow-up took place these clients were omitted from the study. These potential participants would have reinforced the observed findings.

Conclusion

There appeared to be no association between symptoms associated with vitamin B_6 toxicity and high dose vitamin B_6 supplementation. An analysis of the findings indicated that the dose range of 101 – 200 mg demonstrated statistically significant improvements in these symptoms. This is reinforced by evaluating the findings of participants who complained about tingling hands. To conclude, it seems appropriate to suggest a NOAEL of 100 mg per day and a LOAEL of 150 g per day.

Further investigation using double-blind randomized controlled trials is essential to determine safe upper levels for vitamin B_6. A controlled trial which objectively as well as subjectively measure the incidence of peripheral neuropathy is needed. It is crucial to follow-up relevant clients appropriately especially those on long-term B_6 supplementation. Research should also examine the efficacy of using PLP as a vitamin B_6 supplement form.

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