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Characteristics of pyridoxine overdose neuropathy syndrome

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ABSTRACT – A newly recognised neurotoxic syndrome due to pyridoxine (B6) overdose is described. It is the largest series of B6 intoxication hitherto reported. A raised serum B6 level was present in 172 women of whom 60% had neurological symptoms, which disappeared when B6 was withdrawn and reappeared in 4 cases when B6 was restarted. The mean dose of B6 in the 103 women with neurological symptoms was 117 ± 92 mgs, compared with 116.2 ± 66 mgs in the control group. There was a significant difference ($P<0.01$) in the average duration of ingestion of B6 in the neurotoxic group of 2.9 ± 1.9 years compared with 1.6 ± 2.1 years in controls. The symptoms were paraesthesia, hyperaesthesia, bone pains, muscle weakness, numbness and fasciculation, most marked on the extremeties and predominantly bilateral unless there was a history of previous trauma to the limb. These women were taking a lower dose of B6 than previously described (1,2), which may account for the complete recovery within 6 months of stopping B6.

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Severe sensory neuropathy resulting from massive doses of B6 was first described by Schaumburg et al in 1983 (1). The continued promotion of megavitamin therapy has resulted in a milder form of B6 intoxication being found among women taking considerably lower doses of B6. The characteristics of this new syndrome are reported here. The syndrome is limited to those currently taking B6 and whose serum B6 level is raised above the normal range (3.6-18 ng/ml).

Method

All women attending a private practice specialising in premenstrual syndrome who were found to be currently taking B6 were advised to have their serum B6 levels estimated. They were asked if they experienced any altered sensations in their limbs or skin, or if they had noticed muscle weakness or pains. Positive replies were recorded with the patient's description and site of symtoms and a neurological examination followed.

All serum B6 estimations were assayed at Metpath Laboratories, London, using the radioenzymatic assay for pyridoxal-5-phosphate as described by Chabner and Linvingston (3). The normal assay range is 3.16 - 18 ng/ml with an upper limit of sensitivity of 34 ng/ml. All women with raised levels were advised to stop taking vitamin preparations.

Results

A serum B6 level above 18 ng/ml was found in 172 women of whom 103 (60%) complained of neurological symptoms (neurotoxic group) and the other 69 women without neurological symptoms comprised the control group. The serum B6 levels were above the upper limit of testing at 34 ng/ml in 70% of the neurotoxic group compared with 55% of control. The average daily dose of B6 was 117 ± 92 mg in the neurotoxic group compared with 116 ± 66 mgs in controls which is considerably above the recommended daily intake of 2-5 mg daily (Table 1).

The neurotoxic group had taken B6 for an average duration of 2.9 ± 1.9 years, compared with controls 1.6 ± 2.1 years, $P < 0.01$ by Student's t-test. No women in the neurotoxic group had taken

Table 1
Women with neurological symptoms of B6 overdose.

Daily dosage	Neurological symptoms	Controls ($n = 172$)
n	103	69
	%	%
Under 50 mg	20	32
Under 100 mg	38	38
Under 200 mg	31	14
Under 500 mg	11	16
Duration		
	%	%
Under 6 months	0	14
Under 1 year	19	16
Under 2 year	26	20
Under 3 year	20	17
Under 5 year	10	9
Over 5 year	25	24
Age		
	%	%
Under 30 years	7	9
Under 40 years	39	33
Under 50 years	31	38
Over 51 years	23	20

B6 for less than 6 months, whereas 14% of controls had a duration of less than 6 months (Table 1). There was no evidence that the addition of other B vitamins, magnesium or zinc prevented the development of neurological symptoms. The mean ages of the groups were similar, 41.5 ± 8.8 years in the neurotoxic group and 41.9 ± 9.8 years in controls. The reasons for taking B6 were premenstrual syndrome 44%, depression 20%, posthysterectomy syndrome 11%, menopause 9% and a variety of other minor ailments, and no difference was noted between the groups.

On stopping B6 there were no reports of withdrawal symptoms. When retested 2 months later serum B6 levels were within the normal range except for 11 women (controls 4), whose levels were below the normal 3.6 ng/ml. Three months after stopping B6 55% reported partial or complete recovery of neurological symptoms and at 6 months all reported complete recovery. Moreover the areas of hyperaesthesia and numbness noted at the initial examination had disappeared. Seven women in the neurotoxic group inadvertently did not stop B6, they all reported a continuation of symptoms and their serum B6 level remained raised until they discontinued B6.

Three women, who had subnormal serum B6 levels 2 months after stopping B6, were advised to take a daily dose of 50 mg B6, but within a month their serum B6 level rose above normal level and they again experienced symptoms. On stopping B6 all 3 again had subnormal serum B6 levels, which gradually reached normal levels without medication after 4 months. Thereafter, women with subnormal B6 levels were advised to refrain from taking any B6 and when tested 4 months after stopping, their serum B6 levels had reached the normal range.

Case report

A 49-year-woman, who had taken 75 mg B6 daily together with multivitamins, zinc and magnesium for 2 years, and whose serum B6 level was > 34 ng/ml, complained of paraesthesia of hands at night, 'biting ants up her legs, electric shock pains in her head', numbness of her finger tips and itching between the shoulder blades. Examination revealed patchy areas of hypersensitivity to stroking with cotton wool on her back and lower limbs, especially her shins. Reflexes and muscle power were normal, and L'hermitte's test negative. On stopping B6 in July 1985 all symptoms eased within 3 months. She restarted 50 mg B6 in August 1986 and by November 1986 had a return of the same neurological symptoms, the same areas of hypersensitivity and her serum B6 was again > 34 ng/ml. She has again been advised to stop B6.

Characteristics

The neurological symptoms described by the 103 women were paraesthesia, bone pains, hyperaesthesia, muscle weakness, fasciculation and numbness. Symptoms were bilateral in 85%, with unilateral symptoms tending only to occur if the limb had previously suffered trauma (Table 2). These symptoms commonly caused fears of multiple sclerosis, and second opinions had been sought from 2 neurologists, 38 medical consultants and 21 non-medically qualified practitioners.

Paraesthesia was more noticeable at night and limited to the extremeties, with the upper limbs 3 times

	Neurological symptoms in B6 overdose $n = 103$					
	Par-aesthesia	Bone pains	Hyper-aesthesia	Muscle weakness	Numbness	Fasci-culation
Total *n*	59	45	33	33	21	18
	%	%	%	%	%	%
All limbs	39	40	29	21	24	39
upper	46	16	19	30	38	33
lower	15	36	45	49	10	28
Chest	–	7	3	–	–	–
Head	–	2	6	–	28	–
Vagina	–	–	15	–	–	–

more commonly affected than the lower limbs. It was often the first symptom to disappear.

Bone pains were described as lightning, stabbing or shooting, like a knitting needle or electric shocks. The legs were affected twice as commonly as the arms. Although mostly limited to the limbs, nevertheless 3 women complained of shooting chest pains and had all undergone full cardiological investigations with negative results.

Hyperaesthesia was described as burning, crawling, pricking, stinging, itching or 'like a metal scraper'. On examination there was increased sensitivity to pin prick and stroking with cotton wool. Although predominating in the extremities with a stocking-glove distribution, it was occasionally limited to localised areas. When the hypersensitivity was present in the vulva, vagina or nipple it was accompanied by loss of libido causing 2 women to seek help from sexologists. Bacteriological examination of the vagina was negative in all cases.

Muscle weakness was manifested by difficulty in running, lifting, climbing stairs and loss of manual dexterity causing problems with typing, playing the piano, kneading pastry, and maintaining a grip on the steering wheel. Movement was hampered by stiffness, clumsines or a staggering gait. There was no mention of dropping objects. Examination revealed bilateral loss of power and diminished, but not absent reflexes, especially of the ankles. L'hermitte's test was positive in 10 women.

Fasciculation was variously described as twitching, jangling, restlessness, fidgeting and 'movements within'.

Numbness had the stocking-glove distribution on the limbs and 28% also had numbness of the face.

Discussion

This is the first large scale study of neurological symptoms due to B6 overdose in which the serum B6 level has been measured while taking B6, and retested when symptoms improved or were absent. The mean daily dosage used was considerably less than previously reported, which may explain the complete recovery when women in this series stopped taking B6. Schaumburg et al (1) reported 7 patients taking 2 - 6G B6 daily whose sensory neuropathy improved slowly on stopping B6, but without full recovery. In Parry and Bredesen's study (2) 13 of their 16 subjects were taking 2G or more daily and on stopping B6 none resolved completely at follow-up 3 to 18 months later.

The same degree of recovery following cessation of B6 has been reported in animal studies. Thus, administration of moderate doses of B6 to rats or dogs caused ataxia and inability to walk with recovery when B6 was discontinued (4,5); whereas animals receiving extremely high doses of B6 developed ataxia within a few days with destruction of the dorsal root ganglion cells and subsequent degeneration of both dorsal peripheral nerve fibres and dorsal column axons with no recovery.

The duration of drug exposure was greater in this series than in previous reports and appears to have been a significant factor in the development of neurological symptoms, however there may have been

inaccuracy in the patient's recall of the exact dose and duration of B6 intake when the period of ingestion exceeded five years. If duration is an important factor in the development of neurological symptoms it would explain the absence of side effects in reports of double blind controlled trials lasting only a few months (6).

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