Dose response, coasting, and differential fiber vulnerability in human toxic neuropathy: A prospective study of pyridoxine neurotoxicity

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Dose response, coasting, and differential fiber vulnerability in human toxic neuropathy:

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Article abstract—We administered either 1 or 3 g/d of pyridoxine (vitamin B_6) to five healthy volunteers and repeatedly followed serum pyridoxal phosphate levels, clinical symptoms and signs, quantitative sensory thresholds (QSTs), and sural nerve electrophysiology. Pyridoxine was discontinued at the first sign of either clinical or laboratory abnormality. In all subjects, sensory symptoms and QST abnormalities occurred concurrently. Subjects receiving higher doses became symptomatic earlier than low-dose subjects. Elevation of thermal QSTs preceded or exceeded that for vibration in the three low-dose subjects; vibration and thermal QST became abnormal simultaneously in the higher-dose subjects. A reduction in the amplitude of the sural sensory potential lagged behind QST changes in two of three subjects. Symptoms continued to progress ("coasting") for 2 to 3 weeks despite stopping pyridoxine administration and the return of serum pyridoxal phosphate levels to normal. This study suggests that (1) there is a clear dose-percent relationship for pyridoxine-induced neuropathy, (2) QST is a sensitive measurement for detecting early peripheral neuropathy; QST abnormalities may precede changes in nerve conduction studies, (3) coasting appears unrelated to persistently elevated blood levels of the toxin, and (4) a dose-dependent vulnerability may exist among nerve fibers of different caliber when exposed to an axonal toxin, such as pyridoxine.

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The pathogenesis of toxic axonopathies has, by necessity, been elucidated from experimental studies in animals where duration and dose of toxin can be controlled. Certain tenets of neurotoxic disease have been derived from these studies: selective vulnerability of the largest diameter and longest length fibers,[1,2] strong dose-effect and dose-percent relationships with structural damage commensurate with amount and duration of exposure,[3,4] and differing topographic vulnerability within the neuron dependent on dose (eg, distal segments affected by low dose, cell body by high dose).[5-7] It is assumed that these characteristics are relevant to human toxic disease, but controlled studies are lacking.

Pyridoxine (vitamin B_6) is a water-soluble vitamin whose alleged ability to cause selective, reversible, large fiber sensory dysfunction makes it an ideal agent to assess human neurotoxic disease. Humans dosed with pyridoxine develop sensory neuropathy similar to that produced in experimental animals.[4,8,9] In the present study, five volunteers self-administered neurotoxic doses of pyridoxine to determine if the toxic tenets derived from animal studies were true in humans.

Methods. Commercially available pyridoxine was administered orally to five volunteers (four men, one woman) whose ages ranged from 29 to 55 years. All were neurologically normal except subject 2 who had had poliomyelitis as a child. Three *low-dose subjects* (nos. 1 to 3) were given 1 g/d (subjects 1 and 3 = 12 mg/kg; subject 2 = 19.6 mg/kg). Two *high-dose subjects* took 3 g/d (subject 4 = 42.8 mg/kg; subject 5 = 56.9 mg/kg). Pyridoxine was discontinued at the first evidence of sensory disturbance, based on clinical signs and symptoms or laboratory abnormalities. Duration of pyridoxine administration was as follows: subject 1 = 7 months; subject 2 = 4.5 months; subject 3 = 14 months; subject 4 = 3.5 months; and subject 5 = 1.5 months. The study was approved by the Institutional Review Board for Protection of Human Subjects of Montefiore Medical Center.

Periodic clinical and laboratory examinations were performed. The timing of the examinations was, in part, dependent upon the availability of the subject and was not triggered by clinical symptoms. As such, the interval between examinations varied among the subjects. Clinical neurologic examinations included the testing of deep tendon reflexes, appreciation to pin, cold, and vibration, motor strength, and gait. Physiologic evaluations included the following:

(1) Quantitative measurement of the sural sensory

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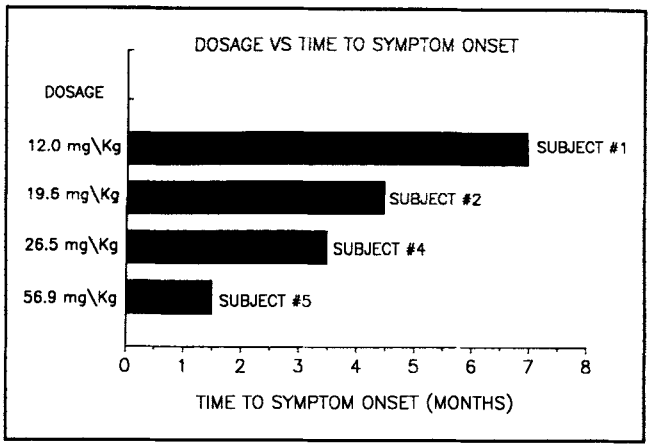

Figure 1. Relationship of duration of pyridoxine administration to onset of sensory symptoms.

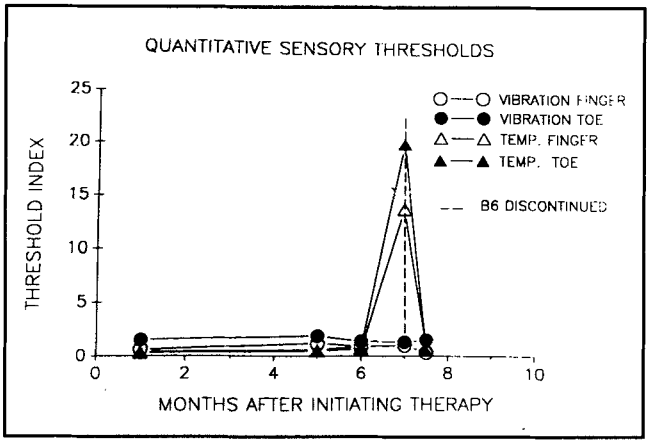

Figure 3. The relationship between vibration and thermal QST levels and time on pyridoxine for subject 1 (low dose).

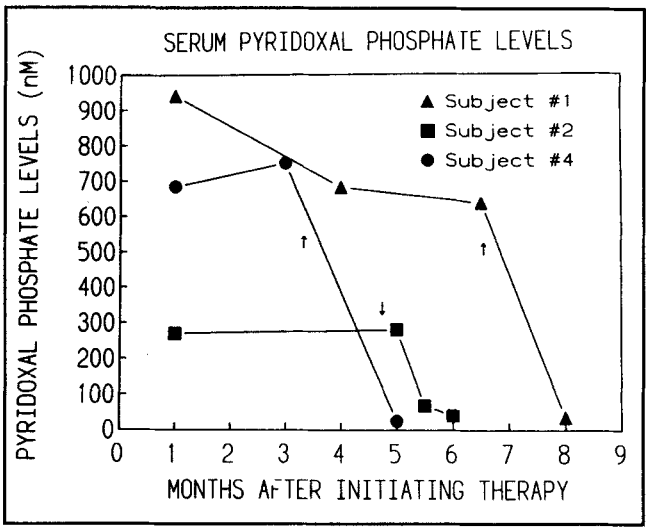

Figure 2. Serum pyridoxal phosphate levels in subjects 1, 2, and 4. Despite return of serum levels to normal, sensory symptoms continued to progress (coasting). Arrows represent when pyridoxine was discontinued.

potential amplitude and conduction velocity, performed in the conventional manner with antidromic recordings. Limb temperature was maintained to at least 33 °C.

(2) Quantitative vibration thresholds, using the Vibratron II (Physitemp Inc, Clifton, NJ), were obtained from the dominant index finger and great toe.[10,11] This machine utilizes 120-Hz vibration and measures vibration threshold to the nearest 0.1 micron. A 2-alternative forced-choice algorithm is utilized. Vibration thresholds reflect function subserved by mechanoreceptors and large-diameter, thickly myelinated sensory fibers.

(3) Quantitative thermal thresholds, using the Thermal Sensitivity Tester (Physitemp Inc, Clifton, NJ), were obtained from the dominant index finger and great toe.[10,12] The thermal tester measures threshold to cold to the nearest 0.1 °C in a range of ±20 degrees from a starting temperature of 25 °C. Thermal thresholds reflect function in small myelinated fibers. Limb temperature for both vibration and thermal threshold testing was kept at 33 °C.

Periodic measurements of serum pyridoxal phosphate were obtained, either from commercial laboratories or from the author's (R.R.) laboratory. The timing of such blood samples was not constant relative to dosing. Thus, serum levels did not represent trough or peak values but were intended only to indicate that the pyridoxine was being absorbed and the duration that pyridoxal phosphate blood levels were elevated after cessation of dosage. The subjects received no other drugs.

Results. *Clinical symptoms.* The initial symptoms in low-dose subjects 1 and 2 were numbness and pins-and-needles sensation of the toes. Subject 2 also noted mild gait imbalance and Lhermitte's sign, all concurrent with the onset of sensory symptoms in the toes. These symptoms occurred 7 months and 4.5 months from treatment onset for subjects 1 and 2, respectively (figure 1). The third low-dose subject (no. 3) never experienced symptoms despite being followed for over 14 months.

High-dose subjects (nos. 4 and 5) initially developed numbness and tingling in the toes concurrent with similar, although less intense, sensations in their fingertips. Mild gait imbalance was reported by subject 4 as an early symptom. Symptom onset ranged from 1.5 months (subject 5) to 3.5 months (subject 4) (figure 1).

Pyridoxine was discontinued within 1 day of symptom onset in all symptomatic subjects. Treatment in patient 3 was discontinued when quantitative sensory threshold (QST) results became abnormal. Despite this, *all* subjects (except no. 3 who never had complaints) reported an *increase in symptom intensity* over the subsequent 2 to 3 weeks ("coasting"). In subjects 1, 2, and 4, symptoms continued to worsen for 2 to 3 weeks despite serum pyridoxal phosphate levels having returned to normal (figure 2). Sensory symptoms gradually resolved—in the low-dose group over 4 to 6 weeks and in the high-dose group over 6 to 8 weeks. All subjects had complete clinical resolution. Clinical examinations remained normal in all subjects, even at the time of maximal symptoms.

Laboratory results. QSTs. The onset of QST abnormalities coincided with the onset of sensory

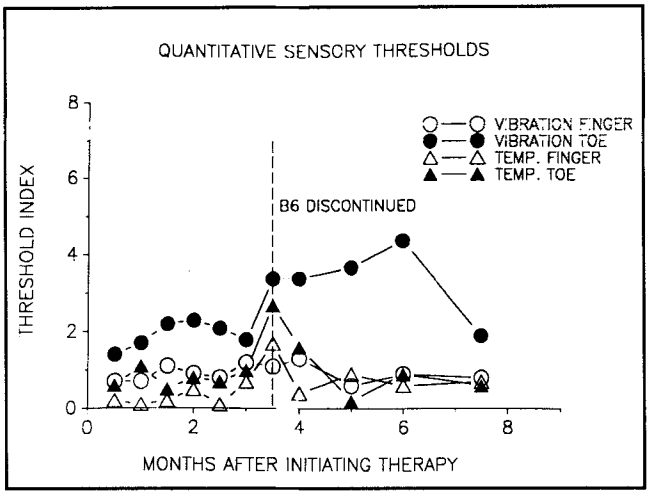

Figure 4. The relationship between vibration and thermal QST levels and time on pyridoxine for subject 4 (high dose). Note progression of dysfunction following discontinuation of pyridoxine.

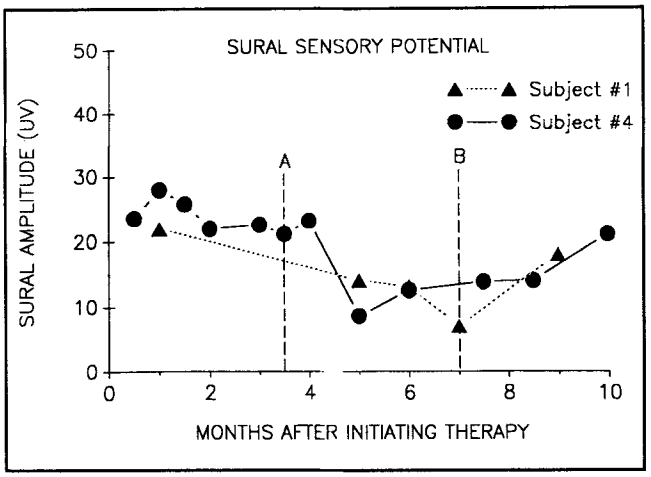

Figure 5. Sural sensory potential amplitudes for subjects 1 (low dose) and 4 (high dose) relative to time on pyridoxine. Points A and B represent the time of symptom onset for subjects 4 and 1, respectively.

symptoms in both high- and low-dose subjects, except subject 3, in whom thermal QST became abnormal without clinical symptoms. Surprisingly, in low-dose subjects, the earliest and most severe QST abnormality was an elevation of the thermal thresholds in the toes (figure 3). At the time of these initial abnormalities of thermal threshold, vibration thresholds were either unchanged or less severely affected. In contrast to the low-dose subjects, in whom elevation of thermal and vibration thresholds was dissociated, high-dose subjects had concurrent and relatively equal elevations of thermal and vibration thresholds (figure 4).

QST values for vibration and thermal sensation continued to deteriorate in high-dose subjects despite discontinuation of pyridoxine. In subject 4, vibration QST progressively worsened over a 2½-month period (three evaluations), although serum pyridoxal phosphate levels returned to normal (figures 2 and 4). In subject 5, vibration and thermal QST continued to worsen 1 month post-pyridoxine (serum levels were not available for subject 5). In low-dose subject 1, vibration and thermal thresholds returned to normal by 1 month post-treatment, and although thermal thresholds returned to baseline by 1 month post-treatment in subject 2, vibration thresholds remained elevated.

Pyridoxal phosphate levels were increased at the time of initial QST elevation (subject 1 = 650 nM, subject 2 = 275 nM, subject 4 = 750 nM), indicating high pyridoxine ingestion and absorption. Despite ingesting a similar dosage as subjects 1 and 2, subject three's pyridoxal phosphate level was only 80 nM. After stopping pyridoxine, pyridoxal phosphate levels continued to be checked. Serum levels returned to normal in subjects 1, 2, and 4 at 4, 2, and 6 weeks, respectively, after dosage was stopped (figure 2). Pyridoxal phosphate levels were not available for subject 5.

Sural nerve electrophysiology. Three subjects (two low-dose [nos. 1 and 3] and one high-dose [no. 4]) had repeated evaluations of sural nerve conduction and sural sensory potential amplitude. In subject 1 (low dose), the reduction in sural potential amplitude accompanied the thermal threshold elevation (figure 5), while in subject 3 (low dose), thermal thresholds were elevated without change in sural potential amplitude. Sural nerve conduction velocities remained unchanged in these subjects. Subject 4 (high dose) had a clear elevation in thermal and vibration thresholds without any accompanying change in sural nerve conduction or amplitude.

Discussion. This study arose as a necessary prelude to a prospective study of the ability of pyridoxine to reduce the symptoms of severe spinal spasticity. Before treating spastic patients with impaired sensation, we deemed it necessary to prospectively study pyridoxine's effects on ourselves. We, along with another volunteer, self-administered the vitamin to correlate serum levels with duration of treatment and onset of neuropathy in individuals with intact sensation. The results obtained confirm earlier experimental and clinical reports that pyridoxine produces a peripheral neuropathy of the distal axonopathy type.

A cardinal finding of this study was that QST measurements proved to be a sensitive laboratory measure of sensory dysfunction. In low-dose subjects, initial QST abnormalities coincided with symptom onset; nerve conductions remained normal in one of the two subjects at this time. Monitoring QSTs proved a powerful and consistent confirmatory measure of sensory dysfunction, which might otherwise have been inapparent had only nerve conduction studies been utilized. In higher-dose subjects, abnormalities of sural nerve amplitude and QST were present concurrently. Clearly, QST measures, which are painless and readily performed by ancillary staff, have an important role in the diagnosis and follow-up of peripheral neuropathy.

The occurrence of a clear dose-percent relationship[3] was strongly suggested by this study. This concept has been suspected in other toxic neuropathies but has been difficult to prove in instances of accidental human exposure. The dose-percent relationship was evident when comparing subjects 1 and 3 who, despite similar mg/kg dosage, had blood levels that markedly differed with consequent disparity in the timing of symptom onset. Serum pyridoxal phosphate levels in subject 1 were over 650 nM compared with values of about 80 nM for subject three. Despite consistent ingestion, subject three's levels were lower than expected; the low levels probably reflect poor gastrointestinal absorption.

Despite discontinuation of pyridoxine, clinical symptoms continued to intensify, most notably paresthesias. This coasting phenomenon occurred in all subjects except subject 3, who was asymptomatic and whose QST abnormalities rapidly resolved with discontinuation of pyridoxine. Subject 2 worsened for 2 to 3 weeks despite the return of serum pyridoxal phosphate levels to pretreatment values. There are suggested explanations for coasting, most notably that the toxin remains stored in either nonneural body tissues, with subsequent release into the blood, or within nerve tissue itself. Pyridoxine is water soluble and not stored in lipid-rich organs; excess intake is rapidly oxidized to 4-pyridoxic acid and excreted. It is therefore unlikely that pyridoxine was sequestered in body organs and subsequently released to the blood. Additionally, despite progressive symptomatology, the serum pyridoxal phosphate levels of subjects 1, 2, and 4 soon returned to normal. These features suggest that clinical progression was not due to a persistently elevated body burden, but either due to toxin remaining in the local nerve environment or, more likely, to persistent neuronal metabolic changes that slowly reversed.

Finally, this study challenges the commonly held notion that pyridoxine and most other axonal neurotoxins preferentially affect only large-diameter, heavily myelinated fibers. This idea was originally derived both from histopathologic analysis of experimental animal studies as well as clinical and electrophysiologic data from humans late in the course of extreme, prolonged megadose intoxication.[1,13] In contrast, our comparatively low-dosed subjects developed small fiber dysfunction that was the earliest or predominant abnormality. Sensory modalities, subserved by large-diameter, thickly myelinated fibers, were either consistently unaffected, affected to a lesser degree, or affected at a later time than small fiber function. With higher doses however, there was coincident large and small fiber dysfunction. Preferential small fiber involvement has been reported in animal studies intoxicated by acrylamide.[14-20] Small fiber dysfunction may have been overlooked in previous studies of human neurotoxic disease, either because such deficits were mild or because they were masked by the concurrent, and clinically more obvious, large fiber dysfunction.

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