PYRIDOXINE INDUCED PERIPHERAL NEUROPATHY A DETAILED REVIEW

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ABSTRACT

Vitamin B6 a water-soluble vitamin, also known as pyridoxine that the body needs for several important functions. It is significant to protein, fat, and carbohydrate metabolism and the creation of red blood cells and neurotransmitters. Pyridoxine (vitamin B6) is a co-factor in many enzymatic pathways involved in amino acid metabolism. It is also recommended as a co-factor to improve the conversion of glyoxylic acid into glycine in ethylene glycol poisoning. Pyridoxine is active in its phosphorylated form of pyridoxal-5-phosphate. Peripheral neuropathy refers to the conditions that result when nerves that carry messages to and from the brain and spinal cord from and to the rest of the body are damaged or diseased. Although the family of B vitamins is often non-toxic, high doses of pyridoxine cause peripheral sensory nerve damage. There are some case reports of sensory neuropathies at doses of less than 500 mg per day in patients taking supplements for months. However, none of the studies had sensory nerve damage at daily intake below 200 mg pyridoxine per day.Thus, intake of doses greater than 100-300mg/d or even 50 mg/d used for longer than 6 months would be deemed harmful.

Keyword:- *Pyridoxine, vitamin B6, Peripheral neuropathy*

1. INTRODUCTION

Vitamin B6, also known as pyridoxine, is a water-soluble vitamin that the body needs for several important functions. It is significant to protein, fat, and carbohydrate metabolism and the creation of red blood cells and neurotransmitters. [1] Pyridoxine (vitamin B6) is a co-factor in many enzymatic pathways involved in amino acid metabolism: the main biologically active form is pyridoxal 5-phosphate. It is also recommended as a co-factor to improve the conversion of glyoxylic acid into glycine in ethylene glycol poisoning. [2]

The neurotoxicity induced by an excess of vitamin B6 in animals has been known for many years but the first human clinical cases have only recently been reported. All subjects showed paraesthesia and numbness as well as ataxia. The clinical examination showed a large sensory deficit with Achilles' reflex loss. The electromyographic examination showed a large sensory wave amplitude decrease but no change in the motor conduction. Different rat models of pyridoxine-induced neuropathy exist. Here, we present results with a modified and improved intoxication schedule of an existing rat model. We describe in detail the evolution of the disease and show for the first time that 4-methyl catechol, an inducer of nerve growth factor (NGF) synthesis, improves the clinical status of the intoxicated animals and restores the morphological integrity of the large fibers. We conclude that: (a) the pyridoxine-induced sensory neuropathy provides the pharmacologists with a valuable model for studying and evaluating new neurotrophic factors endowed with NGF-like properties and (b) this model can be included in the palette of experimental sensory neuropathies used in preclinical research for evaluating new putative neuroprotective drugs, the mechanisms of action of which are not known. [3]

1.1 Clinical role of pyridoxine

Pyridoxine is a form of vitamin B6 used for the prophylaxis or treatment of vitamin B_6 deficiency resulting from conditions such as severe diarrhea, malabsorption, congenital metabolic dysfunction, hyperthyroidism, renal and hepatic disease, congestive heart failure, alcoholism, drug-induced conditions, and during pregnancy and lactation. Pyridoxine-dependent syndromes including pyridoxine-dependent seizures in infants, homocystinuria, pyridoxine-responsive anemia and hyperoxaluria may require the clinical use of pyridoxine as well. Pyridoxine is also an antidote for isoniazid, hydrazine and ethylene glycol toxicities. [4]

1.2 Peripheral neuropathy

In simple terms, peripheral means beyond (beyond the brain and the spinal cord.), neuro -: related to the nerves and -pathy: disease, thus peripheral neuropathy refers to the conditions that result when nerves that carry messages to and from the brain and spinal cord from and to the rest of the body are damaged or diseased. The peripheral nerves make up an intricate network that connects the brain and spinal cord to the muscles, skin, and internal organs. Peripheral nerves come out of the spinal cord and are arranged along lines in the body called dermatomes. Typically, damage to a nerve will affect one or more dermatomes, which can be tracked to specific areas of the body. Damage to these nerves interrupts communication between the brain and other parts of the body and can impair muscle movement, prevent normal sensation in the arms and legs, and cause pain. [5]

2. METHODS

We performed a PubMed search query using the keywords “Pyridoxine AND Peripheral neuropathy”. The search results identified 321 PubMed entries. The abstracts and titles of these entries were discussed and 40 articles were selected and closely reviewed. The criterion for selection of the articles was specifically based on addressing the relationship between pyridoxine and the occurrence of peripheral neuropathy, and the availability of abstract or article.

3. PHARMACOKINETIC DATA OF PYRIDOXINE IN PLASMA AFTER ORAL ADMINISTRATION

In pharmaceutical preparations, pyridoxine or vitamin B6 is generally used as pyridoxine hydrochloride (PN · HCl). [6] Speitling has investigated the metabolism of 600 mg pyridoxine hydrochloride given orally to 9 healthy young males (24 to 31 years of age). [7] Within 0.3 hours after administration (i.e., the first blood sample was drawn) pyridoxine had entered the systemic circulation. Speitling used Bateman's function to describe the entrance of pyridoxine into the central circulation. An apparent first-order absorption rate constant of 2.101 ± 0.513 hour was obtained thereby. This equals a half-life of absorption of 0.354 ± 0.114 hours. Applying Bateman's function is proved by the non-limited absorption of pyridoxine in doses of 600 mg. [8] Therefore procedures of linear pharmacokinetics were applied. Speitling calculated the proportion of pyridoxine, which left the liver in non-metabolized form, to amount to 72- 80% of the dose administered. [7] After oral administration of pyridoxine hydrochloride, its metabolites pyridoxine, pyridoxal 5' -phosphate, pyridoxal, and 4-pyridoxic acid were observed to occur in blood plasma in high concentrations. [7] The slow elimination of pyridoxal 5' -phosphate in its beta-phase explains its accumulation in the human organism and its potential chronic toxicity. [9 - 11] Protein-binding plays a dominant role in the distribution and elimination of the pyridoxine metabolites. Pyridoxal 5' -phosphate is nearly completely protein-bound in plasma, [12, 13] while pyridoxal is only partly bound and pyridoxine exists completely free. [12]

4. PYRIDOXINE ASSOCIATED ADVERSE DRUG REACTIONS AND TOXICITY

4.1 Adverse drug reactions

An adverse drug reaction (ADR) can be defined as ‘an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product’. [14]

Pyridoxine can cause side effects when taken in large doses for a long time. A list of side possible adverse drug reactions associated with pyridoxine includes:[15-16]

- Decreased folic acid

- Decreased sensation
- Headache
- Loss of appetite
- Nausea
- Numbness and tingling
- Neuropathy, somnolence
- Stomach pain
- Unstable gait
- Seizure from a high dose of IV
- Acidosis
- Increased hepatic AST
- Paraesthesia and so on.

Paradoxically the most common symptoms associated with pyridoxine toxicity are similar to those with pyridoxine deficiency. A patient will experience peripheral a swell as sensory neuropathy. Most commonly, this causes numbness in a stocking-glove distribution over the extremities. In addition to peripheral neuropathy, patients can experience ataxia and disequilibrium as well.[17] One large study found that patients also could experience hyperesthesia, bone pains, muscle weakness, numbness, and fasciculations.[18]

4.2 Toxicity

Pyridoxine is used in supra-therapeutic doses as an antidote to treat seizures from isoniazid toxicity. [19] It is used in therapeutic doses for hyperemesis gravidarum and isoniazid. [20,21] It is used as a nutritional supplement by the lay public for a variety of perceived health benefits, including morning sickness, cardiovascular disease, premenstrual syndrome, depression, and carpal tunnel syndrome. Over the counter supplements are the most likely culprit for patients taking in a pyridoxine level above the safe recommended upper limit. Often patients are unaware that high dose pyridoxine could be harmful. Daily dietary intake will not provide enough pyridoxine to cause toxicity. Daily dietary intake of vitamin B6 is approximately 1.9 mg/day in the United States.[22] Pyridoxine toxicity typically manifests as neurologic symptoms, including paraesthesias in the extremities and, in severe cases, difficulty with ambulation. This sensory neuropathy usually develops at doses of pyridoxine above 1000 mg per day. There are some case reports of sensory neuropathies at doses of less than 500 mg per day in patients taking supplements for months. However, none of the studies had sensory nerve damage at daily intake below 200 mg pyridoxine per day. [23]

4.3 Toxicokinetics

After oral ingestion of pyridoxine, peak plasma levels are achieved in approximately one hour. [18] In the liver and other tissues, absorbed pyridoxine forms are converted by the liver to pyridoxal 5'-phosphate (PLP) and transported to in the serum bound to albumin. [24] Oral doses of 100 mg of pyridoxine, pyridoxal, pyridoxamine the majority are excreted unchanged in the urine. [25]

Several drugs have interactions with vitamin B6 and can interfere with their levels. These medications typically lower the level of pyridoxine and leave to vitamin B6 deficiency and not toxicity. Isoniazid, cycloserine, penicillamine, and L-dopa all form complexes with vitamin B6, thus limiting its bioavailability. Oral contraceptives are associated with lower pyridoxine phosphate levels in a subset of women. [26] High doses of pyridoxine may decrease the blood levels of phenytoin and phenobarbital. [23]

4.4 Evaluation

Serum pyridoxine levels are typically less than 30 mcg/L. Patients with signs or symptoms of neuropathy should receive a referral to neurology or other specialists that can perform nerve conduction velocity studies. The diagnostic evaluation will typically start with the patient reporting signs and symptoms of peripheral sensory neuropathy. The workup of peripheral neuropathy is important to evaluate and rule out other etiologies of neuropathy. [27]

5. MECHANISM OF PYRIDOXINE INDUCED PERIPHERAL NEUROPATHY

Pyridoxine is a small water-soluble molecule with a central pyridine ring, a hydroxyl, a methyl, and 2 hydroxymethyl substitutes. Pyridoxine is active in its phosphorylated form of pyridoxal-5-phosphate. It is a

cofactor for a large number of enzymes involved in amino acid metabolism, including decarboxylation, deamination, transamination, and trans-sulphuration of various amino acids [2].

One study examined the role of pyridoxine toxicity on human cells to examine the neurotoxic effects further. They found that pyridoxine induced cell death in a concentration-dependent fashion and inhibited pyridoxal-5-phosphate dependent enzymes.[28] Thus it appears that the inactive form of B6, pyridoxine, competitively inhibits the active vitamin B6 form, pyridoxal-5'-phosphate causing the symptoms of vitamin B6 toxicity to mimic the symptoms of vitamin B6 deficiency.

Although the family of B vitamins is often non-toxic, high doses of pyridoxine cause peripheral sensory nerve damage. [29] Studies on human [18] and rat [5] have shown the effect of pyridoxine toxicity on the soma of dorsal root ganglion (DRG) neurons causing leading to necrosis and broad damage to long myelinated fibers and eventually to cell death. [30] Oxidative stress plays an important role in nerve damage as well as a variety of peripheral neuropathies including oxaliplatin chemotherapy and diabetes-induced neuropathy [31-33]. Furthermore, pro-inflammatory cytokines and the cyclooxygenase-2 (COX2) enzyme, as important inflammatory mediators, may increase various types of nerve damage and neuropathy [34]. Meanwhile, there are free radicals produced by the function of COX-2, which not only augment the oxidative stress but also induce apoptosis in GABAergic neurons [35]. GABA, as an inhibitory neurotransmitter, is synthesized within the presynaptic neurons and is kept in synaptic vesicles. There are two classes of GABA receptors: fast-acting inotropic GABAA and slower-acting metabotropic GABAB receptor [36]. According to the research, the dorsal horn of the spinal cord and sciatic nerve injury lessens the expression levels of GABA and its receptors [37]. Glutamate, as an excitatory transmitter, on the one hand, increases the mGluR5 receptor existing in the DRG and enhances the release of inflammatory components [38] and on the other hand, elevates oxidative stress and apoptosis in cerebral vascular endothelial cells [39].

6. MANAGEMENT

Results showed beneficial effects of Chicory extract on pyridoxine-induced peripheral neuropathy. Modulating of the GABAergic neurotransmitter-mediated reduction of TNF-α may be involved in the anti-neurotoxic and neuroprotective effect of chicory. [40]

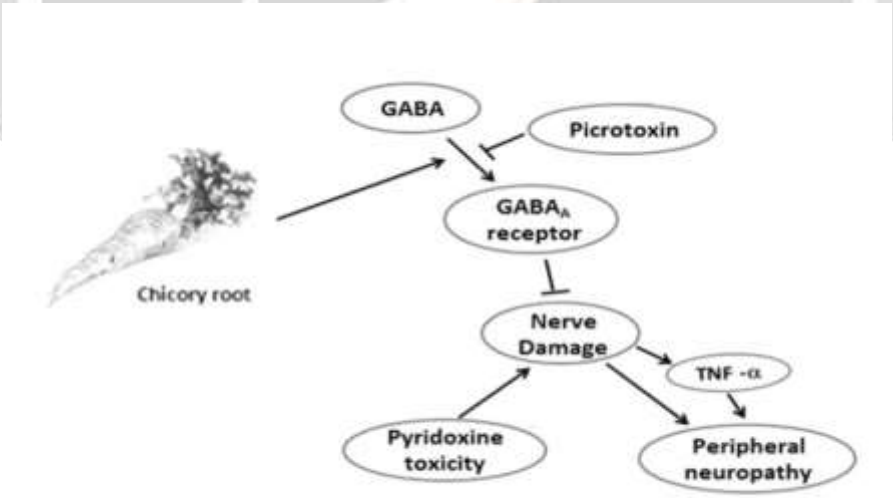

Fig-1: Diagram of chicory mechanism for stimulation and inhibition. [40]

Furthermore, Neurotrophin-3 (NT3) administration prevented the degeneration of sensory fibers in the dorsal column of the spinal cord. These data are consistent with the evidence that NT-3 is a target-derived neurotrophic factor for muscle sensory afferents and suggest that pharmacological doses of NT-3 may be beneficial in the treatment of large-fiber sensory neuropathies. [41]

Recent studies have established that Glucagon-like peptide-1 (GLP-1) and Exendin-4 (Ex4), have multiple synergistic effects on glucose-dependent insulin secretion pathways of pancreatic β-cells and neural plasticity. Data reported here suggest that clinically relevant doses of GLP-1 and Ex4 may offer some protection against

the sensory peripheral neuropathy induced by pyridoxine. The findings suggest a potential role for these peptides in the treatment of neuropathies. [42]

Although pyridoxine-induced neuropathy is transient and can remit after its withdrawal, the process of complete recovery can be slow. Glutamate carboxypeptidase II (GCP II) inhibition has been shown to improve symptoms of both chemotherapy- and diabetic-induced neuropathy. This study evaluated if GCP II inhibition could behaviorally and physiologically improve pyridoxine-induced neuropathy. In the current study, high doses of pyridoxine (400 mg/kg, twice a day for seven days) were used to induce neuropathy in rats. An orally bioavailable GCP II inhibitor, 2-(3-mercaptopropyl) pentanedioic acid (2-MPPA), was administered daily at a dose of 30 mg/kg starting from the onset of pyridoxine injections. Bodyweight, motor coordination, heat sensitivity, electromyographical (EMG) parameters, and nerve morphological features were monitored. The results show beneficial effects of GCP II inhibition including the normalization of hot plate reaction time, foot fault improvements, and increased open field distance traveled. H wave frequency, amplitude, and latency, as well as sensory nerve conduction velocity (SNCV), were also significantly improved by 2-MPPA. Lastly, GCP II inhibition resulted in morphological protection in the spinal cord and sensory fibers in the lumbar region dorsal root ganglia (DRG). In conclusion, inhibition of GCP II may be beneficial against the peripheral sensory neuropathy caused by pyridoxine. [43]

7. CONCLUSIONS

The toxic effects induced by pyridoxine are associated with the dose as well as the duration of administration. Intake of doses greater than 100-300mg/d or even 50 mg/d used for longer than 6 months would be deemed harmful. The tolerable upper limit of pyridoxine for adults is 100mg/day. Although the exact mechanism of toxicity inducing peripheral neuropathy is still not understood, it is recommended that health care professionals remain alert to huge and unexplained intakes of pyridoxine and educate patients regarding its appropriate use.

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