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HIGH-DOSE THIAMINE STRATEGY IN WERNICKE–KORSAKOFF SYNDROME AND RELATED THIAMINE DEFICIENCY CONDITIONS ASSOCIATED WITH ALCOHOL USE DISORDER

Dr. N. Naganikka Assistant Professor, Department of Psychiatry Government Nagapattinam Medical College , Tamil Nadu

Dr Arunkumar K* Assistant Professor, Department of Psychiatry Government Nagapattinam Medical College , Tamil Nadu*Corresponding Author

ABSTRACT Several enzymes connected to human energy metabolism depend on thiamine to function. Through a number of processes, chronic alcohol use is linked to vitamin and thiamine deficiencies. In the setting of alcohol use disorder, thiamine deficiency has been linked to a number of neuropsychiatric disorders, including Wernicke-Korsakoff syndrome, alcoholic cerebellar syndrome and alcoholic peripheral neuropathy. For several neuropsychiatric disorders, high-dose thiamine replacement is advised.

KEYWORDS :

INTRODUCTION

Thiamine, a water-soluble vitamin (B1), is essential for the functioning of a number of enzymes involved in energy metabolism. The active form of thiamine that functions as an enzyme cofactor is called thiamine pyrophosphate (or diphosphate). Adults need 1-2 mg of thiamine day, and this amount depends on how much carbohydrates they consume. If basal metabolic rate is higher, as it is during an alcohol withdrawal condition, for instance, the need rises. Pork (the main dietary source), meat, legumes, vegetables, and fortified foods are some examples of dietary sources. If the diet is poor, the body's ability to store thiamine, which ranges between 30 and 50 mg, will likely be exhausted in 4-6 weeks. The capacity to retain thiamine steadily declines in people who have liver impairment brought on by alcohol.Between 30% and 80% of chronic drinkers have lower thiamine levels. Thiamine shortage is brought on by inadequate vitamin intake, poor intestinal absorption, decreased liver storage capacity, alcohol-induced injury to the renal epithelial cells, which increases renal loss, and excessive loss brought on by medical disorders. Alcohol also affects the quantity of thiamine pyrophosphate that is accessible by decreasing the activity of the enzyme thiamine pyrophosphokinase and decreasing the absorption of colonic bacterial thiamine. Thiamine absorption into cells is further decreased by decreased thiamine pyrophosphokinase activity because enhanced diffusion of thiamine into cells depends on a concentration gradient. In some circumstances (such hypomagnesemia), which are common in alcohol use disorder, impaired thiamine use is observed.This narrative review examines the recommended treatment plans for the neuropsychiatric disorders linked to thiamine deficiency in the setting of alcohol use disorder. To find neuropsychiatric disorders linked to thiamine deficiency in alcohol use disorder patients, a PubMed search was combined with a manual search.

NEUROPSYCHIATRIC SYNDROMES ASSOCIATED WITH THIAMINE DEFICIENCY

Wernicke–Korsakoff syndrome

Chronic alcohol use is linked to Wernicke encephalopathy, which if detected and treated early enough could prevent permanent brain damage typified by the amnestic illness Korsakoff syndrome. Low dosages of thiamine used improperly to treat Wernicke encephalopathy can result in significant mortality rates (20%) and the Korsakoff syndrome in 80% of patients (ranges from 56% to 84%). Oculomotor abnormalities, cerebellar dysfunction, and disorientation make up the standard Wernicke triad. 12.5% of brain samples from people with alcohol dependency contain Wernicke lesions. Only 20%–30% of them, however, had an antemortem clinical diagnosis of Wernicke encephalopathy. It has been discovered that a large number of people experience repeated subclinical episodes of thiamine deficiency, which leads to Wernicke-Korsakoff syndrome (WKS).Only 16% of the 97 chronic alcohol drinkers in an autopsy report exhibited all three of the "classical symptoms," 29% had two signs, 37% had one, and 19% had none. The most frequent indication (found in 82% of cases) is a change in mental state, which is followed by ocular signals (found in 29%) and ataxia (23%). The possibility of WKS should be considered in people who have a history of drinking alcohol and exhibit symptoms such as ophthalmoplegia, ataxia, acute confusion, memory problems, unexplained hypotension, hypothermia, coma, or unconsciousness.Caine et al. have proposed operational criteria for the diagnosis of Wernicke encephalopathy, requiring two of the four features, including (1) dietary deficiency (signs such as cheilitis, glossitis, and bleeding gums), (2) oculomotor abnormalities (nystagmus, opthalmoplegia, and diplopia),(3) cerebellar dysfunction (gait ataxia, nystagmus), and (4)either altered mental state (confusion) or mild memory impairment.

It is wise to have a lower threshold to diagnose Wernicke encephalopathy if any of the clinical indications are present because it is highly challenging to clinically distinguish it from other linked disorders such delirium tremens, hepatic encephalopathy, or head injury. A brain scan using magnetic resonance imaging (MRI) during Wernicke encephalopathy can help with diagnosis since it reveals abnormalities in the medial regions of the thalami and midbrain as well as mamillary body atrophy and an enlarged third ventricle. Most clinical circumstances, though, call for immediate treatment rather than waiting for a neuroimaging result. The recommendations for treatment in the guidelines range greatly. Furthermore, there are very few evidence-based suggestions for using thiamine as a general prophylactic intervention in people with alcohol consumption disorder.The amount and duration of thiamine for WKS have only been examined in a relatively small number of studies, however higher doses might provide a more dramatic response. Eye movement abnormalities (which resolve within days or weeks) and ataxia (which may take months to recover) both show quick improvement with thiamine treatment, although the effects on memory, in particular, are uncertain. The main defining characteristic of Korsakoff syndrome is severe memory impairment. Confabulation, executive dysfunction, flattened affect, apathy, and poor insight are possible early symptoms of the illness. While procedural memory is unaffected, episodic and semantic memory are both impaired.

Thomson et al. proposed that the following people be given thiamine since they are at high risk of developing WKS: (a) all patients who show signs of chronic alcohol abuse and any of the following: Acute disorientation, a drop in conscious level, ataxia, ophthalmoplegia, memory disturbance, and hypothermia with hypotension are all symptoms.(b) Because patients with delirium tremens frequently have Wernicke encephalopathy, each of these patients should be managed, ideally as inpatients; and (c) all low blood sugar patients (who are managed with intravenous glucose) with proof of chronic alcohol ingestion should be given intravenous thiamine instantly due to the risk of acutely provoking Wernicke encephalopathy.

Alcoholic cerebellar syndrome:

Chronic alcohol consumption is linked to anterior superior vermis degeneration, which results in a clinical condition characterised by the subacute or chronic onset of gait ataxia and incoordination in the legs, with relative sparing of the upper limbs, speech, and oculomotor movements. Along with gait ataxia, severe instances have truncal ataxia, mild dysarthria, and upper limb incoordination. Thiamine insufficiency is thought to be the etiological component, while the direct toxic effects of alcohol may also play a role. Although one-third

of patients with persistent alcohol consumption have signs of alcoholic cerebellar degeneration, population-based studies estimate a prevalence of 14.6%.The effect of alcohol on the cerebellum is tiered, with the most severe deficits appearing in long-term and severe alcohol users. Cerebellar degeneration is primarily diagnosed clinically; MRI can be used to evaluate vermian atrophy but is not required. Early involvement of the anterior vermis, followed by involvement of the posterior vermis and adjacent lateral hemispheres later in the course, could be utilised to distinguish alcoholic cerebellar degeneration from other disorders that have more extensive involvement. The severity of cerebellar syndrome is increased in the presence of WKS, suggesting that it is caused by thiamine shortage. As a result, this has been classified as a cerebellar manifestation of WKS and should be treated accordingly.Anecdotal evidence suggests that high-dose thiamine may help with cerebellar syndrome.

Alcoholic peripheral neuropathy:

Peripheral neuropathy is a typical complication of alcoholism, affecting 44% of users. It has been linked mostly to thiamine deficit; however, depletion of other B vitamins (pyridoxine and cobalamin) as well as the direct toxic effect of alcohol have also been linked. Clinically, the emergence of symptoms is slow, with sensory, motor, and occasionally autonomic fibres involved. Neuropathy can impact both tiny and big peripheral nerve fibres, resulting in a variety of clinical symptoms. Thiamine deficiency neuropathy affects bigger fibre types, causing motor impairments and sensory ataxia. Large fibre involvement is evident on examination by distal limb muscular weakness and loss of proprioception and vibratory feeling.These factors, when combined, can contribute to the unsteadiness of gait seen in chronic alcohol users by causing a superimposed steppage gait and diminished proprioceptive input back to the central nervous system's movement control loops. Early symptoms include painful feelings in both lower limbs, occasionally accompanied by a burning sensation or numbness. There is usually a lack of vibration sensation in the distal lower limbs. Later symptoms include proprioception loss, gait disturbance, and reflex loss. The most advanced symptoms include weakness and muscular atrophy. Progression is relatively gradual over months, and upper limb involvement may emerge late in the course.The diagnosis begins with laboratory testing to rule out alternative causes of distal, sensorimotor neuropathy, such as haemoglobin A1c, liver function tests, and a complete blood count to look for red blood cell macrocytosis. Cerebrospinal fluid investigations may reveal elevated protein levels, although they should be normal in cases of alcohol neuropathy and are not indicated for routine assessment. Electromyography and nerve conduction investigations can help determine whether the neuropathy is axonal or demyelinating, as well as whether it is motor, sensory, or mixed. On nerve conduction experiments, alcoholic neuropathy exhibits reduced distal, sensory, and, to a lesser extent, motor amplitudes.Treatments for this syndrome include abstinence and vitamin supplementation, particularly thiamine. In mild-to-moderate situations, near-complete recovery is possible. Thiamine therapy significantly improved alcoholic polyneuropathy in randomised controlled trials.

LABORATORY DIAGNOSIS OF THIAMINE DEFICIENCY

Thiamine and thiamine pyrophosphate levels can be estimated to validate a deficient diagnosis. Thiamine levels in the blood are not accurate indications of thiamine status. A low level of erythrocyte transketolase activity is also beneficial. Values of transketolase of 120 nmol/L have also been used to suggest deficiency, while concentrations of 120-150 nmol/L indicate marginal thiamine status. These tests, however, are rarely regularly conducted since they are time consuming, expensive, and may not be easily available. Because the ETKA assay is a functional test instead of a direct measurement of thiamin status, it may be impacted by conditions other than thiamine deficiency, such as diabetes and polyneuritis.In the absence of laboratory proof of thiamine deficiency, therapy should be commenced. Furthermore, if tests are ordered but the findings are not yet available, therapy should not be postponed. Electroencephalographic abnormalities in thiamine deficient conditions range from diffuse mild-to-moderate slow waves and are not a reliable diagnostic method due to the uneven prevalence of abnormalities among patients.

Surrogate markers that suggest persistent alcohol consumption and nutritional deficiencies other than thiamine may aid in the identification of at-risk patients. This comprises gamma glutamate transferase, an aspartate aminotransferase:alanine transaminase ratio greater than 2, and an increase in mean corpuscular volume. They are helpful when an accurate history of alcohol consumption is unavailable, such as in emergency departments where treatment must begin immediately to minimise long-term repercussions.

THIAMINE REPLACEMENT THERAPY

Oral versus parenteral thiamine

Thiamine absorption in the intestine is dependent on active transport via thiamine transporters 1 and 2, which have saturation kinetics. As a result, the rate and amount of thiamine absorption in healthy individuals is limited. In healthy volunteers, a 10 mg dose results in maximum thiamine absorption, while greater doses have no effect on thiamine levels. As a result, the greatest amount of thiamine absorbed from a dose of 10 mg or greater is between 4.3 and 5.6 mg. However, it has been proposed that, while thiamine transport occurs through an energy-demanding, sodium-dependent active process at physiologic doses, thiamine absorption is primarily a passive process at greater supraphysiologic values. Smithline et al. revealed that oral dosages of up to 1500 mg can result in greater serum thiamine levels.

Because persistent alcohol users have reduced intestinal absorption, absorption rates are likely to be significantly lower. It is around 30% of what is found in healthy people, i.e., 1.5 mg of thiamine is absorbed from 10 mg of oral thiamine. Only 0.8 mg of thiamine is absorbed by persons who consume alcohol and have poor nutrition. The daily thiamine need is 1-1.6 mg/day, which may be higher in people who are alcohol dependent and at risk of Wernicke encephalopathy. Oral thiamine supplementation is quite likely to be insufficient in alcohol-dependent persons who continue to drink. As a result, parenteral thiamine is preferable for replenishment in deficient situations caused by prolonged alcohol consumption. Except in rare cases of allergic responses involving pruritus and local irritation, parenteral thiamine therapy is regarded safe.

There is a modest but significant risk of allergy with parenteral thiamine, particularly when administered intravenously (1/250,000 intravenous shots). Thiamine diluted in 50-100 mg normal saline for infusion may lower the risk. However, parenteral thiamine should always be provided under under supervision and with the requisite resuscitation equipment.

Another critical consideration is the timing of thiamine administration in relation to the progression of alcohol misuse or dependency. Other factors that may influence thiamine administration to patients undergoing alcohol withdrawal include magnesium deficiency, N-methyl-D-aspartate (NMDA) receptor upregulation, and liver dysfunction, all of which may change thiamine metabolism and usage.

Dosing of thiamine:

Because thiamine deficiency is highly common in chronic alcohol users, the need for thiamine increases in active drinkers, and it is difficult to rapidly detect thiamine levels using laboratory testing, all patients, regardless of nutritional status, should be given parenteral thiamine. During inpatient therapy, the dose should be 100 mg thiamine daily for 3-5 days. Multivitamin injections are frequently included to intravenous infusions. Patients at risk of thiamine deficiency should get 250 mg of thiamine intramuscularly daily for 3-5 days, followed by 100 mg of oral thiamine daily.

After around 2 hours of parenteral dosing, thiamine plasma levels drop to 20% of their highest value, shortening the effective "window period" for passive diffusion to the central nervous system. Therefore, Wernicke encephalopathy-like symptoms in thiamine-deficient people should be treated with thiamine three times a day.

Patients who are at risk for Wernicke encephalopathy have been advised to get high-dose parenteral thiamine three times a day. Patients with suspected Wernicke encephalopathy are advised to receive 500 mg of thiamine diluted in 50-100 ml of normal saline infusion over 30 min three times per day for 2-3 days, and occasionally for longer periods, according to a Royal College of Physicians guideline. This programme can be followed until the symptoms go away if there are persistent symptoms including confusion, cerebellar problems, or memory loss. If the symptoms get better, oral thiamine 100 mg three times a day can be kept up for a long time. Alcoholic cerebellar degeneration is also recommended to undergo a similar course of treatment.

Some recommendations call for doses of more than 500 mg intramuscular or intravenous three times a day for 3-5 days, followed

by 250 mg once day for an additional 3-5 days (e.g., British Association for Psychopharmacology).

HOW TO ADMINISTER PARENTERAL THIAMINE WITH PRECAUTIONS

Anaphylaxis monitoring is advised, and there are easily available facilities for resuscitation and treating anaphylaxis, including adrenaline and corticosteroids. Pabrinex, a pair of high-potency vitamins marketed in the UK and containing 500 mg of thiamine (1:250,000 I/V doses), has caused anaphylaxis at a rate of about 4/1 million pairs of ampoules. Thiamine used intramuscularly is said to cause anaphylactic reactions less frequently than intravenous injection. Histamine release that is not specific has been blamed for the reaction. Give intravenous thiamine slowly, preferably by gradual infusion over 15–30 minutes in 100 cc of normal saline.

Conclusion :

It is important to evaluate the risk factors for thiamine deficiency in chronic drinkers. To diagnose thiamine deficient states, including Wernicke encephalopathy, a higher index of suspicion and a lower threshold are required. Other manifestations like polyneuropathy, delirium tremens, and cerebellar syndrome may be caused by thiamine shortage and need to be treated using Wernicke encephalopathy-like protocols. For the treatment of suspected Wernicke encephalopathy and similar diseases, high-dose thiamine is advised. The suggestions, however, are based on limited studies and anecdotal reports and there is a dearth of evidence in the form of randomised controlled trials. However, because thiamine supplementation improves all of these illnesses, it's possible that Wernicke encephalopathy spectrum disorders are a suitable term for them given their shared aetiology.

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