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Mini Review

The Clinical Importance of Vitamin B12

Pereira DSR[1]* and Monteiro MN[2]

[1]Department of Nutrition and Metabolism, Universidade Federal do Amapá, Colegiado de Farmácia, Campus Universitário Marco Zero do Equador, Brazil

[2]Department of Nutrition and Metabolism, Universidad Politécnica y Artística del Paraguay (UPAP), Paraguay

***Corresponding author:** Ricardo de Souza Pereira, Universidade Federal do Amapá, Colegiado de Farmácia, Campus Universitário Marco Zero do Equador, Rod. Juscelino Kubitschek, KM-02, Jardim Marco Zero, CEP68.902-280, Macapá, AP, Brazil

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Abstract

Vitamin B12 is co-factor of enzymes (for example, methionine synthase and methylmalonyl-CoA mutase) which are responsible for catalyzing important biochemical reactions in the human organism. Very high doses of vitamin B12 (milligrams or grams) have medical applications such as cyanide poisoning antidote, gastrointestinal disorders, asthma, migraine, stroke prevention and neurological disorders (Alzheimer's and Parkinson's disease).

Keywords: Vitamin B12; Cyanocobalamin; Gastritis; Pernicious Anemia; GERD; Gastroesophageal Reflux Disease; Cerebrovascular Accident; Beriberi; Scurvy; Pellagra; Pernicious Anemia; Cyanide Intoxication; Hydroxocobalamin; Methylcobalamin; Hydroxycobalamin; Pain; Chronic Pain; Neuropathy; Low Back Pain; Parkinson Disease; Alzheimer Disease

Introduction

What are vitamins?

Vitamins are organic chemical compounds, ie compounds containing carbon. Such substances are necessary for metabolism and therefore are essential nutrients to sustain life. Most vitamins are obtained from food. Vitamins are water-soluble (vitamins B, C) or fat-soluble (vitamins K, E, D and A). The human body can produce vitamin D and vitamin K. Vitamin deficiency can lead to serious medical conditions, as we described below:

Scurvy - Acute or chronic disease due to a lack of ascorbic acid (or vitamin C), characterized by bleeding, gum changes and decreased resistance to infections [1].

Beriberi - polyneuritis due to thiamine (or vitamin B1) deficiency, characterized by sensory and motor disorders (especially lower limb paralysis), circulatory disorders (edema formation, heart problems) and secretory disorders [2].

Pellagra - is a nutritional deficiency caused by a lack of nicotinic acid (also known as niacin, vitamin B3 or PP) or a lack of tryptophan, an essential amino acid. It is more common in underdeveloped countries on a restricted diet and in people with AIDS [3].

Pernicious Anemia-lack of vitamin B12. This vitamin plays an important role in many biological pathways, such as the formation of DNA nucleotides and in DNA methylation. In the clinic, low levels of circulating B12 are defined as <148 pmol/L. Vitamin B12 deficiency can lead to hematological, neurological diseases (Alzheimer´s), and possibly cardiovascular disease. The deficiency occurs worldwide across all age groups in both males and females and stems mainly from poor diet of animal foods and also from intrinsic factors such as malabsorption [4].

Symptoms of Vitamin B12 deficiency anemia

- Diarrhea or constipation.
- Fatigue, lack of energy or dizziness when getting up and straining.
- Loss of appetite.
- Pale skin.
- Concentration problems.
- Shortness of breath, especially during exercise.
- Red and swollen tongue or bleeding gums.

Clinical Uses of Vitamin B12

Antidote against cyanide intoxication

Hydroxocobalamin, a precursor of vitamin B12, has been approved by the Food and Drug Administration (FDA) as an antidote to cyanide poisoning in the United States [5].

Cyanide is an extremely toxic poison that is among the most rapidly lethal poisons known to man. In the absence of prompt and appropriate treatment, exposure to a high dose of cyanide can result in death within minutes due to inhibition of cytochrome oxidase resulting in arrest of cellular respiration [6].

Cyanide poisoning is intoxication that results from exposure to a number of cyanide forms. By burning materials (wool, nylon, polyurethane, silk, cotton, paper and PVC) during a fire, two types of gases are released: Carbon Monoxide (CO) and Hydrogen Cyanide (HCN). Hydrogen cyanide is a combustion product generated in an environment with high temperatures and low oxygen. Statistics in the US show that approximately 80% of fire victims die from toxic smoke inhalation. In addition, cyanide is used in mining, pest control, and industry and has also been used as an agent for suicide, homicide and terrorism [7].

Additional caution (wearing masks, for example) should be taken by coroners who will take autopsy on people killed in fires or whose source of death is not known [8].

Clinical characteristics of hydrogen cyanide poisoning

Rapid breathing, dizziness, weakness, nausea/vomiting, eye irritation, red or pink skin, rapid heart rate, sweating, unconsciousness, respiratory arrest, cardiac arrest, seizures, coma.

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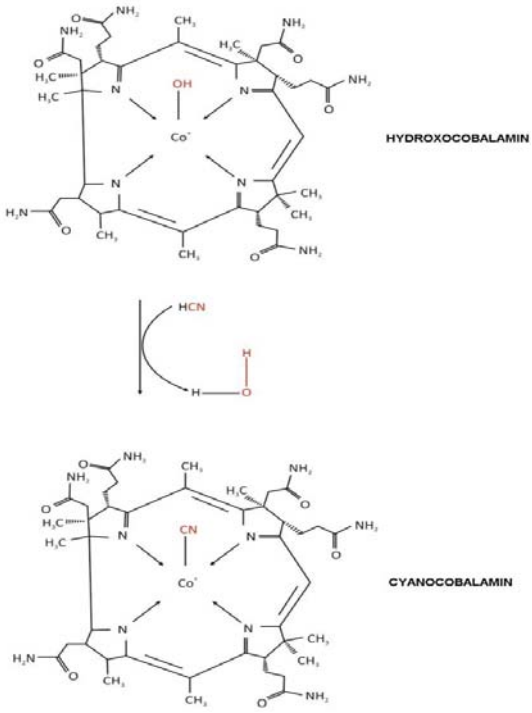

Figure 1: Possible mechanism of action of the transformation of hydroxocobalamin into cyanocobalamin. Cyanocobalamin binds to the cyanide ion to form cyanocobalamin which, in turn, is excreted in the urine [14]. The complete molecule was not designed for didactic reasons.

Low inhaled concentrations or very recent exposure to moderate/high concentrations

Fainting, anxiety, arousal, sweating, dizziness, headache, drowsiness, tachypnea, dyspnea, tachycardia.

Moderate/high concentrations

Prostration, tremors, cardiac arrhythmia, seizures, stupor, paralysis, respiratory coma, depression, respiratory arrest, cardiac arrest, collapse [9].

Cyanide Poisoning

The antidote used in these cases is hydroxocobalamin hydrochloride or hydroxocobalamin acetate, which is a pro-vitamin B12, with very few side effects. In contact with hydrogen cyanide (or hydrocyanic acid), it turns into cyanocobalamin, i.e. active vitamin B12. ADULTS: an intravenous infusion of 5 grams (not micrograms) hydroxocobalamin 5 grams (maximum 15 grams); CHILDREN: 70 mg / kg (maximum dose 5 grams). High survival rate: of 69 patients who inhaled cyanide, 50 survived [10]. In the United States, the FDA has approved Cianokit®. This is the official kit for treating fire victims who have inhaled a lot of smoke or who have inhaled hydrogen cyanide from other sources (attempted murder, acts of terrorism, etc) (Figure 1) [11-13].

Common side effects of hydroxycobalamin may include

- Nausea
- Vomiting
- Diarrhea
- Headache
- Dizziness
- Memory problems
- Restlessness
- Stomach pain
- Acne
- Skin rash or itching
- Red coloring of skin or urine (this may last up to 2 to 5 weeks)
- Warmth or redness under your skin
- Dry throat
- Trouble swallowing
- Hot flashes,
- Injection site reactions (pain, swelling, or irritation of skin), or
- Eye redness or irritation [15].

Asthma

Asthma is a serious public health problem in many countries of the world. Conventional treatments have undesirable effects. Natural treatment with Vitamin B12 has been used since 1952, but unfortunately its use has not become universal [16,17]. An article published in 1989 by Dr. Jonathan Wright on vitamin B12 for the treatment of chronic asthma [18], influenced other researchers to work on the topic [19] and Dr. Shrader to study magnesium and vitamin B12 for treatment of asthma [20].

Recurrent Aphthous Stomatitis

It was demonstrated, in a clinical trial with 58 patients, that 1000 mcg of vitamin B12 a day can regress recurrent aphthous ulcers [21].

Pain Treatment

With the onset of the opioid epidemic, safer pain treatments are needed. Treatment with opioids cause addiction and constipation. First isolated as cyanocobalamin in 1948, vitamin B12 has been used for pain treatment almost since its discovery. Some uses included: low back pain, ulcer pain, diabetic neuropathy, neuralgia [22-26].

Gastrointestinal Disorders

Since 1964, it is known that vitamin B12 deficiency may be involved in chronic atrophic gastritis [27]. Recently, Yang and colleagues used vitamin B12 to treat patients with chronic atrophic gastritis and they correlated the decrease in peripheral neuropathy symptoms in these patients [28].

In 2006, a paper describing a formulation: containing a combination of vitamin B12 (50 µg), vitamin B6 (200 mg), melatonin (2.5 mg), tryptophan (25 mg), methionine (100 mg), betaine (100 mg) and folic acid (10 mg) was able to heal a 6cm giant esophageal ulcer in an HIV positive patient. After 16 years, the patient is still alive and well (Figure 2).

Figure 2: Photographs of the face of a HIV positive patient with an esophageal ulcer of 6 cm (about 3.2 inches) who used the dietary supplementation with vitamin B12, B6, folic acid, melatonin and amino acids in five different time periods (with permission) [8,9]. A: March 2002: Before the ulcer appeared (patient weighed 80 kg); B: October 12, 2003: During the period of the ulcer (patient weighed 40 kg); C: November 14, 2003: After 32 d of treatment (patient weighed 70 kg); D: July 2, 2004: after 9 months of treatment (patient weighing 80 kg); E: October 2018 patient after 15 years of the treatment (weighing 90 kg) [25,29,30].

Alzheimer's Disease and Parkinson's Disease

Vitamin B12 levels in the low-normal subclinical range (<250 ρmol/L) are associated with Alzheimer's disease, vascular dementia, and Parkinson's disease. Vegetarianism and metformin use contribute to depressed vitamin B12 levels and may independently increase the risk for cognitive impairment. Vitamin B12 deficiency (<150 ρmol/L) is associated with cognitive impairment. Vitamin B12 supplements administered orally or parenterally at high dose (1 mg daily) were effective in correcting biochemical deficiency, but improved cognition only in patients with pre-existing vitamin B12 deficiency (serum vitamin B12 levels <150 ρmol/L or serum homocysteine levels> 19.9 μmol/L) (Figure 3) [31].

Migraine

Migraine is the most common form of headache disorder globally. The etiology of migraine is multifactorial, with genetic components and environmental interactions considered to be the main causal factors. Evidences have shown that migraine with aura is associated with elevated plasma levels of homocysteine [32]. Homocysteine catalyzation requires the presence of vitamins B2 (400 mg) B6 (25 mg), B12 (400 μg), and folic acid (2 mg), which can decrease the severity of migraine with aura, making these vitamins potentially useful prophylactic agents for treating migraine with aura [33]. Calik and collaborators found that children with tension-type headache have the serum vitamin B12 level significantly lower than the normal [34].

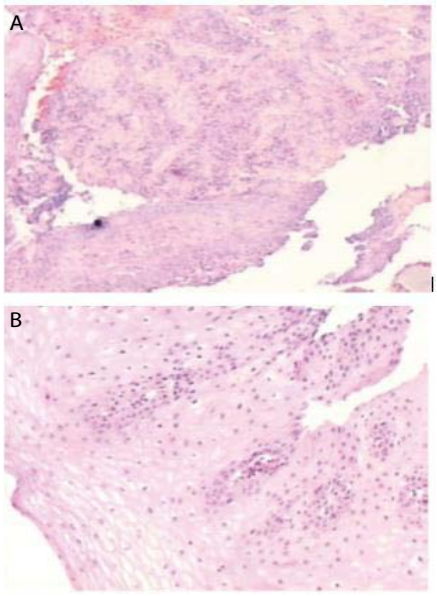

Figure 3: Histological cuttings of a biopsy from a patient with an ulcer of 6 cm (3.2 inches). A: During the period of ulcer; B: After the treatment with vitamin B12, melatonin and tryptophan [25,29,30].

Stroke Prevention

Low levels of vitamin B12, B6 and folate promotes the onset of hyperhomocysteinemia. Excess homocysteine promotes atherosclerosis and induction of thrombosis and, as consequence, increase in risk of heart disease and stroke [35]. Intake of a combination of vitamin B12, B6 and folate, which decreases homocysteine levels, was associated with a significantly lower risk of ischemic stroke [36].

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