VITAMIN B12 (Cobalamin)

Indications

Below are the therapeutic indications for Vitamin B12 (cobalamin):

1) Vitamin B12 (cobalamin) is indicated for cases of macrocytic megaloblastic anemia (pernicious anemia);
2) Vitamin B12 (cobalamin) supplementation is indicated in deficiency states for patients who have undergone gastric resection (gastrectomy), have gastric atrophy, or gastric neoplasms (with insufficient intrinsic factor secretion); in cases of inadequate dietary intake (e.g., vegan diets); and in malabsorption states (such as severe inflammation of the small intestine, resulting in inadequate absorption of the intrinsic factor–vitamin B12 complex);
3) Vitamin B12 (cobalamin) supplementation is indicated in cases of increased physiological demand (e.g., during pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, neoplasia, and renal or hepatic diseases)
4) Vitamin B12 is indicated in the treatment of neuritis and neuralgia, including toxic polyneuritis, dyscrasic polyneuritis, trigeminal neuralgia, cervicobrachial neuralgia, spinocerebellar syndromes, and neurological complications of chronic alcoholism, diabetes, and herpes zoster.

Dosage

Below is the dosage for Vitamin B12 (cobalamin) across various therapeutic indications. In most pharmaceutical preparations, Vitamin B12 is available as cyanocobalamin, which is the most stable form of the vitamin.

Monotherapy

Nutritional Deficiency

Oral administration.

Adults: 50–150 mcg/day of Vitamin B12.

Children: 50–150 mcg/day, divided into three daily doses.

Take Vitamin B12 with meals or within 1–2 hours to minimize the risk of gastric irritation.

Vitamin B12 Deficiency - Macrocytic Megaloblastic Anemia (Pernicious Anemia)

Intranasal Administration.

Adults: 500 mcg of Vitamin B12 (cyanocobalamin) via nasal spray or gel in each nostril once per week. Do not eat or drink one hour before or after intranasal administration. Intranasal therapy can be used as maintenance therapy, provided no neurological symptoms are present, once Vitamin B12 levels are normalized following intramuscular therapy.

Oral Administration.

Adults: Minimum dose of 300 mcg/day of Vitamin B12 (cyanocobalamin).

Children: 60 drops/day (20 drops three times/day) of a solution (containing cyanocobalamin 20 mcg/ml) with meals.

Infants: 40 drops/day (20 drops twice/day) of solution (containing cyanocobalamin 20 mcg/ml) with meals.

In patients with Vitamin B12 deficiency and hematological or neurological abnormalities, oral cyanocobalamin (2 mg/day) has been found to be as effective as monthly intramuscular injections (Butler et al., 2006; Vidal-Alaball et al., 2005; Kuzminski et al., 1998).

Intramuscular Administration.

Adults: 0.2–1 mg of Vitamin B12 (cyanocobalamin or hydroxocobalamin) on alternate days for 1–2 weeks; then 0.25 mg/week until blood values normalize. Maintenance dose: 1 mg once per month.

Children: 1–5 mg of Vitamin B12 (cyanocobalamin or hydroxocobalamin) over a period of 2 or more weeks (each individual dose being 100 mcg). Subsequently, for maintenance therapy, administer 30–50 mcg of Vitamin B12 each month.

Anemic Syndromes

Subcutaneous, Intramuscular Administration.

Adults: 0.5–1 mg/week.

Neurological Syndromes

Subcutaneous, Intramuscular Administration.

Adults: 0.5–1 mg/day.

Vitamin B12 Metabolism Disorders

Intramuscular Administration.

Children: 1 mg/day of Vitamin B12, preferably as hydroxocobalamin, in combination with carnitine and betaine (205 mg/kg/day).

Combinations

Supplements

Vitamin B12 (cyanocobalamin) + Calcium Gluconate + Calcium Heptagluconate

Oral Administration.

Children: 50–100 mcg/day (Vitamin B12) + 0.75–1.5 mg/day (calcium gluconate) + 0.93–1.86 mg/day (calcium heptagluconate).

Vitamin B12 (cyanocobalamin) + Arginine Pidolinate

Oral Administration.

Adults: 150 mcg/day (Vitamin B12) + 900 mg/day (arginine).

Children (up to 6 years): 50 mcg/day (Vitamin B12) + 300 mg/day (arginine).

Children (over 6 years): 100 mcg/day (Vitamin B12) + 600 mg/day (arginine).

Vitamin B12 (cyanocobalamin) + Levoglutamide + Racephosphoserine

Oral Administration.

Adults: 0.4–0.8 mg/day (Vitamin B12) + 60–120 mg/day (levoglutamide) + 60–120 mg/day (phosphoserine) or 500–1000 mcg (Vitamin B12) + 60–120 mg/day (levoglutamide) + 40–80 mg/day (racephosphoserine) or one vial (containing Vitamin B12 0.5 mg + levoglutamide 70 mg + phosphoserine 40 mg) daily.

Vitamin B12 (cyanocobalamin) + Hematoporphyrin

Oral Administration

Adults: 2–4 mg/day (Vitamin B12) + 4–6 mg/day (hematoporphyrin).

Multivitamin Preparations

Vitamin B12 (cyanocobalamin) + Benfotiamine + Vitamin B6 (Pyridoxine)

Oral Administration.

Adults: 500–1500 mcg/day (Vitamin B12) + 100–300 mg/day (benfotiamine) + 150–450 mg/day (Vitamin B6).

Vitamin B12 (cyanocobalamin) + Vitamin B6 (pyridoxine) + Cocarboxylase

Intramuscular Administration

Adults: 0.5 mg/day (Vitamin B12) plus 38.3 mg/day (cocarboxylase) plus 300 mg/day (Vitamin B6); alternatively, 1000 mcg/day (Vitamin B12) plus 25 mg/day (cocarboxylase) plus 100 mg/day (Vitamin B6).

Vitamin B12 (cyanocobalamin) + Vitamin B1 (thiamine)

Intramuscular Administration

Adults: 2 ml/day of solution (containing 1000 mcg of Vitamin B12 plus 25 mg of Vitamin B1).

Vitamin B12 (cyanocobalamin) + Folic Acid + Nicotinamide + Vitamin C (ascorbic acid)

Intramuscular, Intravenous, Slow Venous Infusion

Adults: 714–5000 mcg/day (Vitamin B12) plus 0.2–1.7 mg/day (folic acid) plus 4.5–24 mg/day (nicotinamide) plus 43–300 mg/day (Vitamin C).

Children: 1250–2500 mcg/day (Vitamin B12) plus 0.35–0.7 mg/day (folic acid) plus 6–12 mg/day (nicotinamide) plus 75–150 mg/day (Vitamin C).

Vitamin B12 (hydroxycobalamin) + Vitamin B6 (pyridoxine) + Vitamin B1 (thiamine)

Oral Administration

Adults: 400–800 mg/day (thiamine hydrochloride) plus 600–1200 mg/day (pyridoxine hydrochloride) plus 1000–2000 mcg/day (hydroxycobalamin).

Laxative Preparations

Vitamin B12 (cyanocobalamin) + Cascara + Boldo + Inositol

Oral Administration.

Adults: 50–100 mcg/day (Vitamin B12) + 120–240 mg/day (cascara) + 12–24 mg/day (boldo) + 250–500 mg/day (inositol), to be taken before main meals.

Antianemic Preparations

Vitamin B12 (cyanocobalamin) + Inosine

Oral Administration.

Adults: 0.3 mg/day (Vitamin B12) + 90 mg/day (inosine).

Vitamin B12 (cyanocobalamin) + Calcium Folinate

Oral Administration.

Adults: 2 mg/day (Vitamin B12) + 0.4 mg/day (calcium folinate).

Intramuscular Administration

Adults: 1–4 mg/day (Vitamin B12) plus 0.45–1.8 mg/day (calcium folinate) on alternate days.

Nervous System Stimulants or Nootropics

Vitamin B12 (cyanocobalamn) + Cerebral Phosphatides

Intramuscular Administration.

Adults: 1000 mcg/day (Vitamin B12) plus 12 mg/day (cerebral cortex phospholipids).

Parenteral Nutrition Preparations

Vitamin B12 (cyanocobalamin) + Vitamin B1 (thiamine) + Riboflavin + Nicotinamide + Vitamin B6 (pyridoxine) + Pantothenic Acid + Vitamin C (ascorbic acid) + Biotin + Folic Acid

Intravenous Administration.

Adults and children (weight >10 kg): Administer 10 ml/day of a solution (containing Vitamin B12 5 mcg, Vitamin B1 2.5 mg, Riboflavin 3.6 mg, Nicotinamide 40 mg, Vitamin B6 4 mg, Pantothenic Acid 15 mg, Vitamin C 100 mg, Biotin 60 mcg, and Folic Acid 0.4 mg), appropriately diluted for intravenous use.

Children (weight <10 kg): Administer 1 ml/kg/day of the solution (containing Vitamin B12 5 mcg, Vitamin B1 2.5 mg, Riboflavin 3.6 mg, Nicotinamide 40 mg, Vitamin B6 4 mg, Pantothenic Acid 15 mg, Vitamin C 100 mg, Biotin 60 mcg, and Folic Acid 0.4 mg), appropriately diluted.

Contraindications

Contraindications to the use of vitamin B12 (Cobalamin):

1) Hypersensitivity to vitamin B12 or cobalt
2) Hereditary optic atrophy (Leber's disease) due to the risk of exacerbation.

Warnings

Differential Diagnosis: Megaloblastic anemia caused by vitamin B12 deficiency can also result from folic acid deficiency. It is critical to determine the underlying cause to avoid irreversible progression of neurological symptoms linked to vitamin B12 deficiency, which does not occur with folic acid deficiency. Administration of 0.1 mg/day of folic acid can induce remission of anemia symptoms in patients with vitamin B12 deficiency, and conversely, 10 mcg/day of vitamin B12 may alleviate symptoms in folic acid-deficient patients. In some cases, high-dose folic acid supplementation has worsened anemia symptoms rather than improving them (Johnson, 2007). The recommended limit for folic acid intake from foods and supplements should not exceed 1000 mcg/day (Institute of Medicine, 1998). Other causes of macrocytosis (enlarged red blood cells, a hallmark of megaloblastic anemia) include alcoholism, liver cirrhosis, hypothyroidism, myelodysplastic syndromes, aplastic anemia, iatrogenic factors (e.g., cytotoxic, antiviral, and antineoplastic drugs), and pregnancy.

Monitoring Vitamin B12 Levels: Serum B12 levels should be checked one month after treatment initiation and upon any change, then at intervals of 3–6 months. Serum B12 levels below 200 pg/ml are indicative of deficiency. Homocysteine and methylmalonic acid levels can also indicate B12 deficiency. Homocysteine increases in cases of low B12 levels (>13 µmol/L), though it is a non-specific marker since it is also influenced by vitamin B6 and folic acid. Methylmalonic acid is a more specific marker, as its conversion to acetyl-CoA directly depends on B12; in cases of deficiency, serum methylmalonic acid levels increase (> 0.4 µmol/L) (Klee, 2000).

Elderly Patients: About 10–30% of elderly patients experience some degree of gastric atrophy that may affect intestinal absorption of vitamin B12. In cases of B12 deficiency, supplementing with forms that contain unbound, bioavailable B12 (cyanocobalamin) rather than food-based sources may be beneficial.

G6PD Deficiency: Vitamin B12 in the form of hydroxocobalamin has been associated with hemolytic crises in patients with G6PD deficiency, an X-linked recessive genetic disorder. Patients lacking this enzyme may experience recurrent hemolytic episodes. Various disease variants exist, with the most severe cases causing crises even without triggering factors.

Uremia, Infections, Chloramphenicol, Iron, or Folic Acid Deficiency: These factors may mask or inhibit the response to B12 treatment. In cases of intestinal infection, excessive bacteria may bind to B12 and reduce its absorption.

Oral Contraceptives: Women taking oral contraceptives may show reduced plasma B12 levels (278 vs. 429 ng/ml in contraceptive users vs. non-users) (Lussana et al., 2003). However, supplementation is not typically required in healthy women on oral contraceptives (Mooij et al., 1991).

Hypokalemia, Thrombocytosis: During the normalization of erythropoiesis in patients with severe megaloblastic anemia following B12 therapy, hypokalemia and

thrombocytosis may occur, particularly within the first 24 hours of treatment. Monitoring of plasma potassium and platelet levels is recommended.

Polycythemia Vera: Vitamin B12 deficiency can mask clinical signs of polycythemia vera, which may become apparent upon treatment with cyanocobalamin.

Allergic Rhinitis, Upper Respiratory Infections: Due to limited evidence on the efficacy of intranasal B12 administration in patients with allergic rhinitis or upper respiratory infections, an alternative administration route is advised for these patients.

Autoimmune Thyroid Disease (AITD): Patients with autoimmune thyroiditis are at a higher risk of pernicious anemia (vitamin B12 malabsorption anemia) compared to the general population. In a clinical study, the prevalence of pernicious anemia in patients with low B12 levels (≤133 pmol/L) and high gastrin levels was 31% (Ness-Abramof et al., 2006).

Gastric Neoplasia: Patients with pernicious anemia have three times the risk of developing gastric carcinoma. Pernicious anemia is recognized as a risk factor for gastric cancer, along with H. pylori infection, dietary factors (e.g., high salt intake), smoking, and partial gastrectomy history (Krejs, 2010). Initial endoscopic evaluation is recommended, with follow-ups only in cases of symptoms or histological abnormalities (dysplasia) (screening use of endoscopy remains debated).

Inflammatory Bowel Diseases (e.g., Celiac Disease, Crohn's Disease): Patients with chronic, diffuse intestinal mucosal inflammation may experience reduced B12 absorption with gradual depletion of hepatic stores. In these patients, mild cognitive impairment may represent a long-term indicator of inflammatory bowel disease before the onset of megaloblastic anemia.

Gastrointestinal Surgery: Patients who have undergone gastric or small intestinal resection should be closely monitored postoperatively for B12 levels and provided with supplements if necessary.

Gastric Abnormalities Associated with Pernicious Anemia: In patients with pernicious anemia, elevated gastrin levels (16.5% of cases), reduced pepsinogen I (22%), achlorhydria (29%), and antibodies against gastric parietal cells (23%) may occur (Juncà et al., 2006). Gastrin levels are often high (>1000 pg/ml) due to lack of control by hydrochloric acid, whose production is reduced/absent in gastric atrophy.

Vegetarian Diets: Individuals following strict vegetarian diets excluding meat, fish, eggs, and dairy should take B12 supplements or consume B12-fortified foods (e.g., enriched cereals) to avoid deficiency. Infants breastfed by women on strict vegetarian diets (e.g., vegan diets) are particularly at risk for B12 deficiency within months of birth, which can have severe physical and neurological consequences (Kaiser, Allen, 2008; von Schenck et al., 1997).

Pregnancy: Vitamin B12 is essential, and its requirement increases during pregnancy. Daily intake recommendations rise from 2 mcg to 2.2 mcg (Italian Society of Human Nutrition recommended nutrient intake). Adequate intake is advised.

Lactation: B12 concentration in breast milk corresponds to serum levels.

Energy Supplements: B12 supplementation has not been shown to enhance physical performance in individuals with adequate dietary intake (Lukaski, 2004).

Interactions

Colchicine, p-Aminosalicylic Acid, Alcohol (High Quantities): Prolonged use of these substances (for over two weeks) may cause malabsorption of vitamin B12. In patients on extended treatment with p-aminosalicylic acid or on high-dose colchicine, monitoring serum vitamin B12 levels is recommended (Davis, 1985).

Chloramphenicol: This antibiotic may delay or disrupt reticulocyte response (reticulocytes are direct precursors to erythrocytes, constituting about 2% of circulating red blood cells) to vitamin B12 supplementation.

Phenytoin, Phenobarbital, Primidone: These anticonvulsant medications have been associated with reduced vitamin B12 absorption. In patients undergoing treatment with these drugs, diminished B12 availability could contribute to neurological side effects. Ensuring adequate vitamin B12 intake is advisable for patients on phenytoin, phenobarbital, and primidone.

H2-Receptor Antagonists (Cimetidine, Famotidine, Ranitidine) and Proton Pump Inhibitors (PPIs) (Omeprazole, Lansoprazole, Esomeprazole, Pantoprazole, Rabeprazole): These agents can reduce the absorption of food-sourced vitamin B12 but not that in supplements. Vitamin B12 in food, protein-bound, requires hydrochloric acid for release to bind with intrinsic factor. Since H2 antagonists and PPIs decrease gastric acidity, they may interfere with the release of "free" vitamin B12 (Bradford, Taylor, 1999; Howden, 2000). The vitamin B12 in supplements is already in "free" form. B12 deficiency can occur in patients on long-term high-dose PPI therapy (Valuck, Ruscin, 2004); the risk appears lower with H2 antagonists, mainly in patients with inadequate B12 stores (Termanini et al., 1998; Force, Nahata, 1992). Monitoring B12 levels is recommended in long-term, high-dose PPI therapy.

Cobalt Radiation: Cobalt radiation exposure may reduce intestinal absorption of vitamin B12 (McBrien, 1973).

Metformin: This medication has been linked to decreased vitamin B12 absorption. Possible mechanisms include altered gastrointestinal motility, bacterial overgrowth, and interference with calcium-dependent absorption of the B12-intrinsic factor complex (Liu et al., 2006; Buvat, 2004; Bauman et al., 2000). In a study of patients with type 2 diabetes treated with metformin (850 mg three times daily) or placebo for approximately four years, a 19% average reduction in B12 levels was observed. There was an absolute risk of B12 deficiency (<150 pmol/L) of 7.2% (p=0.004), with a number needed to treat (NNT) of 13.8 for 4.3 years, and an absolute risk for low B12 levels (150-220 pmol/L) of 11.2% (p=0.001) with an NNT of 8.9 for 4.3 years. The B12 reduction correlated with elevated homocysteine, a cardiovascular risk factor (14.9 vs. 18.1 vs. 23.7 micromol/L in patients with normal B12, low B12, and deficient B12 levels, respectively) (De Jager et al., 2010). Diabetic patients with B12 deficiency may face an increased cardiovascular risk due to the combination of diabetes and hyperhomocysteinemia. Regular monitoring of plasma B12 levels in diabetic patients on metformin is advised.

Neomycin: Oral neomycin administration may decrease B12 absorption (Davis, 1985).

Nicotine: Nicotine may decrease vitamin B12 absorption (Piyathilake et al., 1994).

Potassium: Certain potassium salts (chloride and citrate) may reduce B12 absorption.

Nitrous Oxide: Nitrous oxide can oxidize and inactivate B12. Patients with subclinical B12 deficiency undergoing nitrous oxide anesthesia may develop neurological symptoms indicative of B12 deficiency—sensory neuropathy, myelopathy, encephalopathy—days or weeks post-exposure. In individuals with normal B12 levels, the effect of nitrous oxide is generally negligible. It is recommended to assess B12 levels before nitrous oxide anesthesia.

Ion-Exchange Resins (Cholestyramine, Colestipol): These cholesterol-lowering resins may reduce intestinal absorption of B12 bound to intrinsic factor. In vitro, cholestyramine has not been shown to absorb "free" B12 (Leonard et al., 1979; Andersen, Schjonsby, 1978). In pediatric patients on cholestyramine (2.5-year follow-up), no variations in B12 levels were reported.

Vitamin C: Preliminary data suggest that vitamin C supplementation may negatively impact B12 absorption, though iron and nitrates appear to mitigate this effect. Allow at least one hour between the intake of these two vitamins.

Side effects

Side Effects Observed in Clinical Trials with Patients Treated with Vitamin B12 (Cyanocobalamin, Hydroxocobalamin) via Intramuscular Route

Cardiovascular: Heart failure, pulmonary edema, peripheral vascular thrombosis.

Dermatological: Acneiform eruption, pruritus, transient rash. Iatrogenic acne (drug-induced) is characterized by the absence of comedones, sudden onset, and involvement of atypical skin areas (as opposed to the face, back, and chest).

Hematological: Polycythemia vera. Polycythemia vera is a hematopoietic stem cell disorder characterized by excessive proliferation of red blood cells, and to a lesser extent, granulocytes and platelets.

Gastrointestinal: Moderate and transient diarrhea.

Systemic: Generalized feeling of swelling; anaphylactic reactions, which can progress to shock and death.

Side Effects Observed in Clinical Trials with Patients Treated with Vitamin B12 (Cyanocobalamin) via Intranasal Route

Respiratory System: Rhinitis.

Central Nervous System: Headache, paresthesia.

Gastrointestinal: Glossitis, nausea.

Systemic: Asthenia, infections.

Toxicity

Overdose: In cases of high doses of vitamin B12 (cyanocobalamin), the excess amount is eliminated through urine without causing toxic effects due to accumulation. In clinical trials, administration of 0.4 mg for 40 months and 1 mg for 5 years has not been associated with adverse effects (Liebson, 2006). Reports of allergic reactions, acne, and exacerbation of psoriasis have been documented.

Reproductive Toxicity: There are no available in vivo studies or human data regarding the effects of vitamin B12 (cobalamin) on reproductive capability and embryofetal toxicity. Consequently, the FDA has classified vitamin B12 as a Class C drug for use during pregnancy. This classification includes medications for which studies in women are not available, and studies in animals have shown harmful effects on the fetus (teratogenic, lethal, or otherwise), or medications for which no studies exist in either humans or animals. Class C medications should only be administered if the potential benefits justify the potential risks to the fetus. Vitamin B12 is an essential vitamin, and since the requirement increases during pregnancy, adequate intake is recommended.

Pharmacology

Vitamin B12 (cobalamin) (INN: Cyanocobalamin) is a water-soluble vitamin that is inactivated by light and heat. Its chemical structure is characterized by a porphyrin ring with a cobalt atom at the central position, to which a nucleotide and a variable residue are attached, resulting in different forms of cobalamin: cyanocobalamin and hydroxocobalamin are the forms available for therapeutic use (of the two, cyanocobalamin is the most stable); methylcobalamin and deoxyadenosylcobalamin are the forms present and utilized within the cell. Thus, vitamin B12 can be viewed as a vitamin complex, specifically referred to as the vitamin B12 complex.

The daily amount of vitamin B12 for the adult and pediatric populations, according to the Recommended Daily Allowance (LARN) set by the Italian Society of Nutrition, is listed below (guidelines 1996):

Infant (up to 12 months): 0.5 mcg/day

Child (age < 4 years): 0.7 mcg/day

Child (age < 7 years): 1 mcg/day

Child (age < 11 years): 1.4 mcg/day

Adult, child (age > 11 years): 2 mcg/day

Pregnancy: 2.2 mcg/day

Lactation: 2.6 mcg/day

The recommended levels of vitamin B12 (RDA, Recommended Dietary Allowances) indicated by the American Institute of Medicine are slightly higher (Institute of Medicine, 1998):

Infant (0-6 months): 0.4 mcg/day

Child (7-12 months): 0.5 mcg/day

Child (age < 4 years): 0.9 mcg/day

Child (age < 9 years): 1.2 mcg/day

Child (age < 14 years): 1.8 mcg/day

Adult, child (age > 14 years): 2.4 mcg/day

Pregnancy: 2.6 mcg/day

Lactation: 2.8 mcg/day

Vitamin B12 (cobalamin) is synthesized by bacteria, including the intestinal flora, which produces a minimal amount, as well as by fungi and algae; it is not synthesized by animals or plants. Because the absorption of vitamin B12 requires the presence of a glycoprotein known as intrinsic factor, secreted by the parietal cells of the stomach, vitamin B12 produced by intestinal flora cannot be absorbed as it cannot bind to intrinsic factor. Vitamin B12 that is bound to intrinsic factor is absorbed in the

distal ileum. The binding capacity of intrinsic factor can be saturated: after oral administration of 500 mcg of vitamin B12, approximately 10 mcg is absorbed (Carmel, 2008); with higher doses, the absorbed amount significantly decreases.

The daily loss of vitamin B12 (approximately 0.15%) is replenished through the diet: meat, particularly liver, fish, eggs, milk, and dairy products. In foods, vitamin B12 is bound to proteins and requires hydrochloric acid and gastric protease to become available for absorption. In fortified foods and supplements, vitamin B12 is added as cyanocobalamin in its "free" form.

Vitamin B12 (cobalamin) accumulates in the liver (adult individual: 3000-5000 mcg) and is present in trace amounts in feces and urine. The amount in urine increases significantly when vitamin B12 is administered parenterally in high doses, exceeding the liver's storage capacity and the transportable amount by the specific plasma protein, transcobalamin II.

Within the cell, vitamin B12 acts as a coenzyme for folate in DNA and RNA synthesis reactions. A deficiency in vitamin B12 results in cell division arrest. The cells most affected by this condition are those with a high turnover rate, such as bone marrow cells (macrocytic megaloblastic anemia) and gastrointestinal epithelial cells (glossitis, aphthous ulcers, diarrhea, malabsorption). Additionally, since vitamin B12 is involved in lipid metabolism, a deficiency is also associated with neurological symptoms (demyelinating neuropathy).

In the bone marrow, a lack of vitamin B12 (cobalamin) is evidenced by an increase in the number and size of red blood cell precursors (megaloblasts) and a reduced number of mature elements. In the blood, circulating erythrocytes appear larger (macrocytosis) but are weaker and more fragile (macrocytic megaloblastic anemia). In severe cases, megaloblastic anemia may progress to pancytopenia. Neurologically, vitamin B12 deficiency can cause irreversible damage due to demyelination of the posterior and lateral columns of the spinal cord (funicular myelosis). Neurological symptoms include paresthesias, loss of proprioception and vibration sense, memory loss, confusion, irritability, vision loss, delusions, hallucinations, and psychosis.

The biochemical reactions involving vitamin B12 (cyanocobalamin) as a coenzyme include the conversion of methylmalonyl-CoA to succinyl-CoA (active form of vitamin B12: adenosylcobalamin) and the conversion of 5-methyl-tetrahydrofolate and homocysteine to tetrahydrofolate and cysteine (active form of vitamin B12: methylcobalamin).

The first reaction, the transformation of methylmalonyl-CoA to succinyl-CoA, is a crucial step in fatty acid synthesis; succinyl-CoA then enters the Krebs cycle, through which the cell produces the energy it requires for survival, and is involved in hemoglobin synthesis. In the absence of vitamin B12, methylmalonyl-CoA accumulates, leading to the formation of abnormal fatty acids that deposit in phospholipid membranes. The presence of these fatty acids is likely partially responsible for the neurological effects associated with vitamin B12 deficiency.

In the reaction converting homocysteine to methionine, an essential amino acid, tetrahydrofolate is concurrently formed, representing the form in which folic acid can

be utilized by the cell from its precursor, 5-methyl-tetrahydrofolate. Folic acid derivatives are essential in the synthesis of purine bases, which, together with pyrimidine bases, are components of the structure of DNA and RNA. Methionine plays a role in the synthesis of choline, phospholipids, and the basic protein of myelin; S-adenosylmethionine serves as a universal methyl donor (CH3 groups) for substrates, including DNA and RNA, hormones, lipids, and proteins. A lack of vitamin B12 leads to the accumulation of both homocysteine and unusable folate (the accumulation of 5-methyl-folate is also referred to as the "methyl trap" because folate is trapped as a methylated derivative). This reaction represents the intersection between the biochemistry of cobalamin and that of folic acid, explaining why folic acid supplementation may partially correct the non-neurological symptoms of megaloblastic anemia due to vitamin B12 deficiency (megaloblastic anemia can also be caused by a deficiency of folic acid). Since, despite folic acid intake, neurological symptoms persist, it is important to determine whether megaloblastic anemia is due to a lack of folic acid or vitamin B12; in the latter case, inadequate therapy would lead to the progression of neuronal toxicity to an irreversible stage (Montgomery et al., 1981).

Because vitamin B12 deficiency results in the accumulation of homocysteine, elevated levels of this amino acid serve as a marker for both genetically based alterations in vitamin metabolism and conditions of deficiency (Fowler et al., 2005). Elevated homocysteine levels constitute an independent cardiovascular risk factor and have also been linked to Alzheimer's disease and cognitive capacity in elderly patients without dementia (Refsum et al., 2006; Clarke et al., 1998; Seshadri et al., 2002). Hyperhomocysteinemia has been shown to be a pro-thrombotic factor, reducing endothelial function, promoting lipid peroxidation, and smooth muscle cell proliferation, and has been associated with coronary artery disease and stroke (Clarke et al., 2007; Refsum et al., 2006; Refsum et al., 1998; Siri et al., 1998; Malinow, 1995; Selhub et al., 1995).

It has been hypothesized that supplementation with B vitamins, specifically B6 and B12, and folic acid, by reducing homocysteine levels, could influence cognitive function in elderly patients. However, studies conducted in both demented and non-demented patients have yielded conflicting results (Aisen et al., 2008; Clarke, Bennet, 2008; Durgan et al., 2007; Schulz, 2007).

In the cardiovascular domain, based on available studies, supplementation with vitamin B12, B6, and folic acid to reduce homocysteine levels has not proven effective in lowering cardiovascular risk in the male population for secondary prevention and in high-risk females (those with previous cardiovascular events or at least three cardiovascular risk factors), despite the reduction in homocysteine levels (SEARCH Collaborative Group, 2010; Albert et al., 2008; Ebbing et al., 2008; Lonn, 2008; Bonaa et al., 2006; American Heart Association Nutrition Committee, 2006; Lonn et al., 2006; LicToole et al., 2004).

In adult person, the amount of vitamin B12 (cobalamin) stored in the liver and the fact that the vitamin undergoes enterohepatic recirculation (the amount excreted with bile is reabsorbed in the intestine) allows for the coverage of any dietary

deficiency for several years before evident clinical symptoms appear. Children, on the other hand, who have a lower reserve quantity, are more susceptible to the toxic effects of vitamin B12 deficiency due to dietary causes (e.g., vegetarian diets). The elimination of meat and dairy from the diet (vegan "vegetarian" diet) during childhood (up to 6 years) has been associated with vitamin B12 deficiencies and lower responses in cognitive tests compared to children who were treated in their early years with a complete diet (Louwman et al., 2000).

Other causes of reduced vitamin B12 intake include primary reduction or absence of intrinsic factor (genetic or autoimmune pernicious anemia) or secondary causes (removal of the stomach, atrophic gastritis) and malabsorption due to diverticulosis of the small intestine, ileitis, ileocolic fistulas, ileal resection (Crohn's disease), tropical sprue (a disease of unknown etiology characterized by malabsorption and alterations of the small intestine mucosa), proliferation of Gram-negative bacteria with stasis of intestinal contents, presence of parasites (e.g., diphyllobothriasis, infection by fish tapeworm), or iatrogenic causes (from medications) (Festen, 1991). A deficiency of vitamin B12 can also be caused by reduced intake when the need increases: pregnancy, hyperthyroidism, hemolytic anemia, hemorrhage, carcinomas, kidney, and liver diseases. More rarely, vitamin B12 deficiency can be due to congenital defects in the intestinal absorption site (the vitamin B12-intrinsic factor complex is absorbed through an active transport mechanism).

The Schilling test measures the absorption and renal excretion of radiolabeled vitamin B12 (cyanocobalamin) and helps direct the diagnosis in cases of deficiency. In patients with pernicious anemia, the addition of exogenous intrinsic factor leads to increased absorption and excretion of the vitamin. If, however, the cause of the hypovitaminosis is an inflammatory condition affecting the ileal wall or sprue, the lack of cobalamin absorption will be independent of the addition of exogenous intrinsic factor.

Vitamin B12 (cyanocobalamin) deficiency manifests as fatigue, asthenia, mood swings, memory loss, weakness in the limbs, difficulty walking, tingling, and paralysis. Pharmacological treatment involves the administration of vitamin B12 via injection. If the vitamin B12 deficiency is due to an underlying treatable condition, vitamin supplementation continues until normal levels of the vitamin are achieved; if the deficiency is not resolvable (e.g., insufficient secretion of intrinsic factor, genetic anomalies related to the absorption site, etc.), treatment must continue for life.

When the deficiency of vitamin B12 arises from defects in its metabolism, clinical signs appear in the early stages of the child's life and are accompanied by delays in both physical and neurological growth. In the first year of life, the child struggles to feed, presents an overall weight/height growth below the norm, experiences psychomotor delays, seizures, and microcephaly. Subsequently, mental retardation, deficient psychosis, and spasticity arise, alongside microangiopathic thrombosis in the circulatory system, causing multiorgan damage due to repeated ischemias. Treatment involves the parenteral administration of vitamin B12, preferably in the form of hydroxocobalamin, at a dosage of 1 mg/day, in combination with carnitine and betaine (250 mg/kg/day) (Sghirlanzoni, 2004).

In therapy vitamin B12 is administered as cyanocobalamin or hydroxocobalamin; hydroxocobalamin binds more significantly to plasma proteins (transcobalamin), allowing it to remain in the bloodstream longer. The pharmacological response to vitamin B12 supplementation is rapid: within 48 hours, the bone marrow appears normal, reticulocytosis begins after 2-3 days, and hemoglobin levels start to rise within the first week, normalizing within 1-2 months.

Some studies have highlighted a deficiency of vitamin B12 in children affected by gastrointestinal pathogens, including Helicobacter pylori and G. lamblia. It is not known whether in these children the pathogen causes the vitamin deficiency due to malabsorption or whether insufficient intake of vitamin B12 promotes the colonization of these bacteria (Shuval-Sudai, Granot, 2003; Olivares et al., 2002).

Moreover, vitamin B12 seems to protect against rotavirus infection, an enteropathogen responsible for acute diarrhea in the pediatric population (Long et al., 2007).

Pharmacokinetics

Vitamin B12 (cobalamin) is introduced into the body via diet (primarily animal-based foods); the recommended daily amount is approximately 2–2.5 mcg for adults and adolescents and 0.5 mcg for infants, with an increased intake during pregnancy and lactation.

No significant differences in bioavailability have been observed between oral and sublingual administration of vitamin B12 (Sharabi et al., 2003).

Vitamin B12 (cyanocobalamin) is absorbed in the small intestine in the presence of an intrinsic glycoprotein (molecular weight 50,000), known as intrinsic factor, produced by the stomach, and calcium ions. The amount of vitamin absorbed as the vitamin B12-intrinsic factor complex ranges from 1.5 to 3.5 mcg, depending on the administered dose, decreasing as the dose increases. The absence of intrinsic factor prevents vitamin B12 (cyanocobalamin) absorption.

In dietary sources, vitamin B12 is protein-bound and requires hydrochloric acid and gastric proteases to release it for absorption. In supplements, vitamin B12 is already in its free form, such as cyanocobalamin or hydroxocobalamin, with comparable bioavailability and absorption.

The vitamin B12-intrinsic factor complex is absorbed in the distal ileum (small intestine) via an active transport mechanism. Disruptions in the absorption site or carrier prevent the absorption of intrinsic factor-bound vitamin B12, leading to a deficiency state (pernicious anemia).

When administered orally in patients with gastric atrophy or pernicious anemia, a small portion of the vitamin B12 dose (1%) is absorbed via passive diffusion (Lederle, 1991).

Following intranasal administration, the peak plasma time was approximately 1.25 (+/- 1.9) hours, with a peak plasma concentration of 757.96 (+/- 532.17) pg/mL. Bioavailability was approximately 6% compared to that observed with intramuscular administration; bioavailability with nasal spray was about 10% lower than that achieved with nasal gel.

The serum concentration of vitamin B12 is typically between 200 and 900 pg/mL.

In the bloodstream, vitamin B12 is transported bound to a specific protein, transcobalamin II; with high doses of vitamin B12, any amount exceeding the transport capacity of the serum protein is excreted in the urine. After administration of 50 mcg of vitamin B12, 80–90% is retained in the body; after 100 mcg, this percentage drops to 55%, and to 15% following administration of 1000 mcg.

Despite being water-soluble, vitamin B12 (cobalamin) accumulates in the liver, which serves as a “storage site”; in an adult male, the liver can contain up to 3000–5000 mcg of vitamin B12. Thus, in conditions of insufficient dietary intake, the quantity of vitamin stored in the liver is capable of buffering the deficiency for a prolonged period, with a delay of several years before clinical symptoms of hypovitaminosis appear in

adults. In children, however, dietary deficiency (e.g., from a vegetarian diet) leads to hypovitaminosis symptoms more rapidly.

Vitamin B12 (cyanocobalamin) undergoes enterohepatic circulation: 80% of the portion excreted via bile is reabsorbed in the intestine.

Vitamin B12 (cyanocobalamin) crosses the placenta and can reach fetal concentrations similar to maternal levels.

Approximately 30–60% of a dose of vitamin B12 (cyanocobalamin) is excreted in the feces.

Half-life: 1–4 years.

Classification

Chemical formula

$C_{63}H_{88}CoN_{14}O_{14}P$

Molecular weigh

1355.38

ATC code

A06AB57

A11DB

A11JA

A12AX

A13A

B03BA01

B03BA51

B05XC

N06BX

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