Cyanocobalamin (Vitamin B12) Injection

General Information

Cyanocobalamin is a vitamin of the B-complex family, commonly known as cobalamins (corrinoids). It is a synthetic or man-made form of vitamin B12 that is available as both a prescription and over-the-counter (OTC) medication. Cobalamins exist in several other chemical forms, including hydroxocobalamin, methylcobalamin, and adenosylcobalamin.[1,2] Cyanocobalamin is the most common form of cobalamins used in nutritional supplements and fortified foods. It contains a cyano (cyanide) group in its structure, which makes it more stable than other forms of vitamin B12 as the cyanide stabilizes the molecule from deterioration. Hydroxocobalamin, however, is the most biologically active form of Vitamin B12; hence, it is more preferable than cyanocobalamin for the treatment of vitamin B12 deficiency.[1,2,3,4]

Cyanocobalamin does not naturally exist in foods owing to the presence of cyanide, which is absent in the natural form of the vitamin. The chemical structure of cyanocobalamin contains the rare mineral cobalt (4.34%), which binds the cyano group and is located in the center of a corrin ring.[5] The commercial manufacturing of the vitamin is done through bacterial fermentation. Compared to other forms of vitamin B12, it is easier to crystallize and more air-stable.[3] Cyanocobalamin is usually obtained as a dark red, amorphous or crystalline powder, orthorhombic needles, or red crystals. The anhydrous form of the compound is highly hygroscopic. It may absorb up to 12% of water if exposed to air. Cyanocobalamin is sparingly soluble in alcohol and water (1 in 80 of water), but insoluble in chloroform, acetone, and ether. The coenzymes of this vitamin are highly unstable in light.[6]

Cyanocobalamin is available in several dosage forms including the tablet, nasal spray, and injection. The US-FDA initially approved the drug in 1942.[7] However, the compound became widely available for routine use in the treatment of B12 deficiency in the early 1950s.[8]

Mechanism of Action

Cyanocobalamin is a vital compound for cell division and growth, hematopoiesis, and nucleoprotein and myelin synthesis. This vitamin also has an important role in protein synthesis, neural metabolism, DNA and RNA production, as well as fat and carbohydrate metabolism. Several cells appear to have the greatest demand for cyanocobalamin, particularly those that undergo rapid division such as bone marrow and epithelial cells.[5,7]

Cyanocobalamin binds itself to plasma proteins in the systemic circulation. It attaches with specific cobalamin binding proteins, called transcobalamin I and II, to enter into the tissues. In cells, this vitamin functions as a cofactor for two vital enzymatic reactions: (1) methionine synthase, i.e. the regeneration of methionine from homocysteine and (2) methylmalonyl-CoA mutase, i.e. the isomerization of methylmalonyl-CoA to succinyl-CoA. Both these methylation reactions are vital for growth and cell reproduction.[9,10]

Methionine, a sulfur-containing, essential amino acid, is a precursor of S-adenosylmethionine, a cofactor for one-carbon metabolism and the final methyl donor for the methylation of DNA, RNA, proteins, and phospholipids.[11] The methionine synthase plays a paramount role in the synthesis of nitrogenous bases (purines and pyrimidines) involved in the formation of DNA. The lack of adequate cobalamin in the body hinders the regeneration of tetrahydrofolate, which eventually leads to megaloblastic anemia due to the functional folate deficiency.[9,10] On the other hand, the

methylmalonyl-CoA mutase helps to metabolize odd chain fatty acids and branch chain amino acids.5 Cobalamin is also thought to keep the body's level of sulfhydryl (SH) groups in reduced form. SH groups activate many enzyme systems involved in protein synthesis as well as fat and carbohydrate metabolism. If there is a lack of cobalamin in the body, methylmalonyl CoA accumulates, which presumably leads to the neurological manifestations of B12 deficiency.47912

The replenishment with parenteral cyanocobalamin causes a rapid and complete improvement of megaloblastic anemia and gastrointestinal symptoms caused by vitamin B12 deficiency. The parenteral administration also halts the progression of neurological damage associated with B12 deficiency, but the complete improvement of the condition may depend on the severity and extent of the deficiency.1213

Pharmacokinetics

***Absorption**:* The oral absorption of vitamin B12 occurs exclusively in the terminal ileum of the small intestine. This absorption, however, almost entirely depends on intrinsic factor (IF) for transition through the stomach. IF is a glycan containing protein secreted by parietal cells (oxyntic cells) located in the gastric mucosa. Vitamin B12 separates from IF in the terminal ileum if sufficient calcium ions are present.414 It then enters the gastrointestinal mucosal cells, attaching itself with transcobalamin I and II for transportation to the various tissues. A small amount, approximately 1.2% of the orally administered dose, is absorbed passively without IF.9 This passive absorption is adequate only when cobalamin is administered at high doses (i.e. >1 mg). Oral doses of < 3 mcg can take up to 8 to 12 hours to reach peak plasma concentrations, as the lower ileum temporarily retains the compound.15

The absorption of parenteral cyanocobalamin doses occurs quickly and quantitatively from their sites of injection. The compound reaches the blood quite immediately, as the parenteral route allows rapid absorption through diffusion, bypassing the intestinal barrier. The plasma concentration of cyanocobalamin gets to its peak around 1 hour after intramuscular (IM) injection.16

***Distribution**:* Cyanocobalamin is distributed to tissues by transcobalamin II. The liver is the main organ that stores this vitamin, converting it as coenzyme B12. The half-life of the compound in the liver is about 400 days. The estimated total body stores of cobalamin ranges from 1 to 11 mg in healthy individuals. The liver stores about 50 to 90% of it. The bone marrow also serves as a storage for the absorbed vitamin B12. Enterohepatic recirculation (biliary recycling) preserves systemic stores.1517

***Metabolism**:* Cyanocobalamin is metabolized in the liver. Following its binding with IF, the cobalamin-IF complex promotes hepatic uptake via an active and saturable mechanism called cubilin/AMN receptor-mediated endocytosis. The complex is then absorbed into enterocytes, breaking down IF in the lysosome. Cobalamin is then exported out of the cell by the transporter ABCC1. It then passes through the liver's portal vein, finally reaching the systemic circulation. Endothelial cells mediate the storage of vitamin B12 in the liver.171819

***Excretion**:* The elimination of cyanocobalamin primarily occurs through the bile, which secretes around 3-8 mcg of the compound into the gastrointestinal tract per day. All but approximately 1 mcg is reabsorbed in patients with adequate IF.7 Excess vitamin B12 remains unchanged and is excreted as such in the urine. Within 48 hours of injecting a 100 or 1000 mcg dose, 50-98% of the compound may be excreted in the urine via glomerular filtration. The large portion of urinary excretion occurs within the first 8 hours.16 The storage of cyanocobalamin in the body is dose-dependent. When an IM dose is about 80-90%, the body retains up to 50 mcg of the

compound; however, the retention can drop to 55% if a dose of 100 mcg is administered.20 Intravenous administration of cyanocobalamin provides less chance for liver storage because of more rapid excretion than IM or subcutaneous doses.16

Contraindications/Precautions

Cyanocobalamin is contraindicated in those with hypersensitivity to cobalt moiety or cobalamin molecule due to the risk of anaphylaxis.21

Warnings:

The use of cyanocobalamin is warned in patients with early Leber's disease as there have been reports of severe and swift optic atrophy with its administration. Appropriate caution should be exercised while treating severe megaloblastic anemia with cyanocobalamin as intense treatment may lead to hypokalemia and sudden death. Cautious use of parenteral cyanocobalamin is also recommended in patients with renal impairment, including premature neonates, because of the possibility of greater aluminum accumulation, which may cause central nervous system and bone toxicity. Formulations of cyanocobalamin injection containing benzyl alcohol as a preservative should also be avoided in premature neonates and those with hypersensitivity due to its association with 'gasping syndrome.151620

Monitoring:

A history of the patient's allergies/hypersensitivity should be obtained before administering cyanocobalamin injection. If the patient is suspected to be sensitive to cobalt or other components of cobalamin, an intradermal test dose is recommended.1215

Several laboratory tests should be performed prior to treatment with cyanocobalamin, including serum vitamin B12, folate, iron, hematocrit, and reticulocyte count. All these parameters need to be normal before initiating the treatment. Serum levels of vitamin B12 and peripheral blood counts should be monitored in one month. For hematocrit and reticulocyte counts, recommendations are to repeat these tests daily from the 5th to 7th days of treatment and then frequently until the hematocrit returns to a normal range.91622

Both serum potassium concentrations and the platelet count need to be monitored carefully after parenteral administration of cyanocobalamin. This is because hypokalemia and thrombocytosis could occur due to the increase in erythrocyte metabolism following vitamin B12 therapy. Potassium replacement therapy should be administered if necessary.1215

Patients with pernicious anemia are three times more likely to have gastric carcinoma compared to general population; thus, appropriate tests need to be carried out to rule out this condition if suspected.16

Therapeutic response to cyanocobalamin may decrease due to elderly age, infection, renal insufficiency, diabetes mellitus, marrow suppressants use (e.g. chloramphenicol), and concurrent iron or folic acid deficiency.1223 Therefore, these factors should be taken into consideration and regular monitoring should be performed in these conditions while treating vitamin B12 deficiency with cyanocobalamin.

Adverse Reactions/Side Effects

Vitamin B12 is known to be non-toxic even in high doses. The reported adverse reactions following parenteral administration of vitamin B12 include:

- **Generalized**: Anaphylaxis and death
- **Cardiovascular**: Pulmonary edema and congestive cardiac/heart failure during early treatment; peripheral vascular thrombosis
- **Hematological**: Polycythemia vera (a rare type of blood cancer)
- **Gastrointestinal**: Mild, transient diarrhea
- **Dermatological**: Itching; transitory exanthema (widespread skin rash)
- **Miscellaneous**: Feeling of swelling of entire body

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