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DEFICIENCY OF VITAMIN B_{12} LEADING TO VARIOUS DISEASED CONDITION, ITS DOSAGE FORM AND TREATMENT

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ABSTRACT

Most of the time it is unclear with the type of dosage form in treating vitamin B_{12}deficiency. Main cause of vitamin B12 deficiency is malabsorption syndrome and nutritional deficiency.Absorptionof vitamin B12 is a complex processand dependent on multiple factors such as salivary binder, gastric secretion of acid, intrinsic factors, pancreatic exocrine sufficiency and intact terminal ileal mucosa. Disruption of any of these factors lead to vitamin B12 deficiency. If untreated leads to pernicious anemia (Biermer's disease)and atrophic gastritis. Vitamin B 12 deficiency manifests neurological and hematological disorder.Various vitamin B12 dosage forms are available in market to treat deficiency like tablet, capsule, injections, nasal sprays, buccal patches. Well, the type of dosage form as a supplement for deficiency depends on the type of diseased condition, age and the dose required.The deficiency is treated with initial high oral therapy dose of 500 µg/day for 4-6 weeks whereas injection therapy with dose of 1000-1500 µg/day for 6-8 weeks. Initial high dose therapy is followed by maintenance treatment, if vitamin B12 deficiency is due to diet related than 250 µg/day (oral), if insufficient then 500 µg/day (oral), and for absorption disorder is 1000 µg/day (oral) and injection dose is 1000 µg/month. Vitamin B12 deficiency is commonly observed in elders above 60 years and senile age[2,4,8,12,14,16].

Keywords: Dosage form, vitamin B12,deficiency, treatment, dose and anemia.

INTRODUCTION

Vitamin B_{12} also known as Cobalamin, is a generic name, is a water-soluble vitamin present in various food like fish, meat, seafood, dairy products and cereals. Primarily two bioactive forms of vitamin $B_{12}$are methyl-cobalamin and adenosyl-cobalamin which is naturally present in food. Methyl-cobalamin is used by methionine synthase to produce amino acid methionine from homocysteine. Cyanocobalamin and hydroxocobalamin (also called hydroxyl-cobalamin) are synthetic form of cobalamin.Vitamin B12 is necessary for various biological functions like RBC production and cellular metabolism like DNA synthesis, mitochondrial metabolism. It is also involved in various biological functions[1,7,8,16].

Vitamin B12 use and function-Apart from use to treat pernicious anemia, cobalamin can also be used to treat age related cognitive decline with vitamin B 12 deficiency, age anemia of pregnancy, Alzheimer's disease, age relatedhearing loss, sickle cell anemia, vitiligo, low back pain, cystic fibrosis with vitamin deficiency, diabetes, sleepdisorder, cyanide poisoning, inherited cobalamin disorder, osteoporosis, restless leg syndrome, pregnancy support, sickle cell anemia, cardiovascular health, , neural tube defects, neurological function including cognition, depression, schizophrenia, multiple sclerosis. Vitamin B12 is effective in breaking down the higher levels of homocysteine thus reduces the chances of heart disease[1,11,14].

Signs and symptom for deficiency: Weakness, fatigue, pale yellow skin, changes in mobility, depression, confusion and memory loss, poor blood clotting, sensation of needles (nerve damage), breathlessness, dizziness, mouth ulcers, disturbed vision, high temperature, skin sensitivity. Vitamin B12 deficiency is mostly observed in patients with malabsorption syndrome or metabolic disorders, gastric atrophy, inflammatory bowel disease, exposed to metformin more than four months or use of H_2 blockers more than 12 months, a person with strict vegan diet, nitrous oxide induced megaloblast[1,5,6,7].

It is commonly observed in geriatric (above 75 years) patients.

Recommended daily dose of vitamin B12:[8]

Low dose – 10 µg
Medium dose – 250 µg
Increased dose – 500 µg
High dose – 1000 µg
Mega dose – 5000 µg

Recommended dietary allowance[7,8,14]

Toddlers

0-6 months – 0.4 µg
6 months- 1 year– 0.5 µg

Children:

1-3 years – 0.9 µg
4-8 years – 1.2 µg
9-13 years – 1.8 µg
14-18 years – 2.4 µg
Adults: 2.4 µg
Pregnancy – 2.6 µg
Lactation – 2.8 µg

INTRAMUSCULAR INJECTION

Intramuscular injection of B12is the traditional treatment for treating deficiency and pernicious anemia. It offers low retention time than buccal formulation. Recommended I.M dose for pernicious anemia is 1000 µg/day for one week. For nutritional deficiency of vitamin B 12,cobalamin single dose of 500 µg once a week is recommended. Similarly, it has several advantages; avoids first pass metabolism so drug reaches directly into systemic circulation and hence dose required is less. Parenteral injections may lead to skin condition like acne, dermatitis. Nutritional deficiency can be treated with I.M injection of cobalamin with single of 500 µg once a week or as required. It has several disadvantages like intramuscular injection is painful, difficult to treat disabled patient, self-administration is difficult so health care professional is required hence cost effective, dangerous in patients with anticoagulation[3, 9].

Dosage

Intramuscular injection (cyanocobalamin or hydroxyl-cobalamin)

- **Adults**
  Initial
  - 30mcg daily for 5 to 10 days.
  - Maintenance: 100-200 mcg every month.

- **Children**
  - **Initial**
    1000-5000 mcg, given in single daily dose of 100 mcg over 2 or more weeks.
  - Maintenance: 60 or more mcg per month.

Dosage adjustment

Dosage adjustment, as needed to normal hematologic morphology and erythrocytic count greater than 4.5 million/mm^{-1}

To treat familial selective B12 malabsorption- Intramuscular injection (cyanocobalamin)

Adults
Initial
1 mg per week
Maintenance
250 mcg per month

To treat hereditary deficiency of transcobalamin Ⅱ Intramuscular injection (CYANOCOBALAMIN)

Adults-1 -2 mg per week

To treat cyanide poisoning: I.M injection of 1 gm/sol of hydroxocobalamin.

To treat pernicious anemia: Initial: 250-100mcg I.M injection of hydroxy-cobalamin alternate day for 1-2 weeks, followed by 250 mcg weekly until normal count

Maintenance: 1000 mcg I.M inj. Once in 2-3 month.

Consumption of hydroxocobalamin to treat megaloblastic anemia of pregnancy, lead to deformity in infant[8].

VITAMIN B12 TABLET

To treat vitamin B12 deficiency caused by nutritional intake imbalance, tablets (extended release tablet, chewable tablet, rapid dissolving tablet) capsule and lozenges are preferred as prescribed.

Dose intake in individual is based on the severity of deficiency in adults and children. Recommended oral dose to treat pernicious anemia is 1000 µg/day for 1-4 week.As absorption by oral route requires intrinsic factor for proper absorption. Along with cyanocobalamin, oral absorption promotor, salcaprozate sodium, hydroxocobalamin can be used as it reaches higher peak plasma

concentration when used in combination to treat vitamin B12 deficiency and anemia.
Clinical trial recommends 1500 µg of cobalamin in combination with 5 µg folate for 2 years for osteoporosis lowers homocysteine which significantly reduces hip fracture. Traditionally intramuscular injection was the primary mode to treat pernicious anemia and oral route was a support to the treatment, recently oral route or tablet form of 1-2 mg/day cobalamin can be used to treat severe form of vitamin B12 deficiency[13,15].

CYANOCOBALAMINE

Different dose of Cyanocobalamin according to the requirement to treat pernicious anemia available are tablet (100mcg, 250mcg, 500mcg, 1000mcg), extended release tablet (1000mcg),Sublingual (2500mcg), Injectable (1000mcg/mL),Nasal spray (500mcg per spray)
Cyanocobalamin in Infants (Recommended daily requirement)-
0-6 months – 0.4 mcg
6 months- 1 year– 0.5 mcg
1-3 years – 0.9 mcg
4-8 years – 1.2 mcg
9-13 years – 1.8 mcg
>14 years – 2.4 mcg

To treat B12 deficiency

Initial- 0.2mcg/kg for 2days, followed by 1000mcg/day for week, followed by 100mcg/day for week, then 100mcg/day for month.
Maintenance- 100mcg I.M/S.C monthly[8,7].

BUCCAL PATCHES

This dosage form provides convenient and attractive administration due to its flexibility and thickness. It shows rapid onset of action due to rich blood supply in buccal mucosa and avoids first pass metabolism. Buccal patches give local effect, offering site specific release of drug on mucosa; and systemic effect involves drug absorption through mucosal barrier to reach systemic circulation.
Major drawback is the absorption of drug due to its unintended swallowing hence mucoadhesive films can be applied which provides longer time drug concentration. Buccal patches are placed on the floor of mouth in sulcus region between alveolar margin and cheeks.Pernicious anemia is treated with buccal patches as maximum absorption occurs directly into the blood stream[2,3].

CAPSULE

Capsule is the most popular form of vitamin B12 supplement. As no additives are added it is advantageous with high purity. It usually contains only one pharmaceutical ingredient along with plant base cellulose. It ranges from 3-5000mcg. Anemic patients with absorption disorder are treated with 1000 – 2000 mcg of cyanocobalamin. Nutritional deficiency can be overcome with 1mcg of cyanocobalamin in case of patients with fully functional gastro intestinal tract[18].

NASAL SPRAY

Provides faster absorption of hydroxocobalamin reaching maximum plasma cobalamin level. The only approved formulation approved by FDA consist of low concentration cyanocobalamin in isotonic saline solution or lactose powder. Though it was safe and effective, no clinical practice was followed as results obtained were inconvenience.
Nasal gel with dose of 400-500 mcg of cyanocobalamin was claimed to be effective. Cyanocobalamin is contraindicated in patient with amblyopia and simultaneous tobacco usage and perniciousanemia with optic neuropathy hence hydroxocobalamin is a drug of choice[16,17,18].

CONTRADICTION BETWEEN DOSAGE FORMS

Intramuscular injection is the primary treatment for severe type of pernicious anemia over tablet or oral dosage form as it results in reduction of RBC. 1000 mcg/day I.M injection for one week gives same response as 1000mcg/day tablet for 1-4 week. Intramuscular is painful, inconvenient, costly compare to oral administration. Tablet dose of 1000-2000mcg/day is as effective as 500mcg/day of intramuscular injection. Buccal films are preferred over adhesive tablets in terms of flexibility, thickness, maximum absorption into blood stream and high drug concentration is achieved but it may result in unintended swallowing[3,4,13].

CONCLUSION

As absorption of cobalamin is complex, intramuscular, subcutaneous, buccal patches are preferred over tablets. Oral and intranasal route of administration is not indicated until the major symptoms are resolved in pernicious anemia. Oral tablets can be usedin combination with oral absorption promotor (salcaprozate) to increases absorption rate. Vitamin deficiency due to malabsorption can be treated with parenteral or nasal spray whereas pernicious anemia initially treated with parenteral therapy, here nasal or oral dosage form is not indicated until patient achieves hematologic remission and no signs

of CNS involvement. Large single oral dose of tablet 1-2 mg/day of cobalamin is effective to treat the most severe type of pernicious anemia.Nasal sprays provide fast and adequate absorption through nasal mucosa and leads to sustained increased in baseline cobalamin concentration.

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