COMPARISON STUDY OF VITAMIN-B12 FOR ITS EFFICACY AND BIOAVAILABILITY OF VARIOUS FORMULATIONS IN THE TREATMENT OF PERNICIOUS ANEMIA

KUSHALI JAIN D*, JAYANTHI C, MAHAVEER SINGH, ROOPA G, K. HANUMANTHACHAR JOSHI

ABSTRACT

Vitamin B12 helps your body to use fat and carbohydrates for energy and makes new protein. It is also important for normal blood, cells, and nerves. Most people get enough vitamin B12 in their diet, but a deficiency may occur in certain health conditions (e.g., poor nutrition, stomach/intestinal problems, infection, cancer). Serious Vitamin B12 deficiency results in anemia and nerve damage if left untreated. Vitamin B12 deficiency usually treated by parenteral and oral dosage forms, but these routes of administration is associated with absorption and compliance issue. More recently, it has been demonstrated that the function of this missing intrinsic factor is to aid the absorption of Vitamin B12 and deficiency termed as pernicious anemia. Pernicious anemia may be satisfactorily treated by parenteral administration of the extrinsic factor. Vitamin B12 is only slightly absorbed when given by mouth to patients with pernicious anemia, but a hematological response may be obtained if relatively large doses are given by this route. The objective of this study was to compare the efficacy and safety profile of appropriate vitamin B12 formulation in the treatment of pernicious anemia.

Keywords: Vitamin B12, Oral, Buccal, Intra muscular, Intrinsic factor, Pernicious anemia.

INTRODUCTION

Vitamin B12, or Cobalamin, is a water-soluble vitamin present in foods of animal origin, such as meat, poultry, fish, seafood, eggs and milk products. Some foods are also fortified with vitamin B12, with the exception of algae; very few plants contain this vitamin. In addition, the quantities present in plants are low and in a form that may be inactive or not easily absorbed by the body. Many people around the world suffer from vitamin B12 deficiency. Vegans, people living in developing countries, pregnant women and older adults are more at risk of Vitamin B12 deficiency [1]. Vitamin B12 is also used for memory loss, Alzheimer’s disease, boosting mood, energy, concentration and the immune system; and slowing aging. It is also used for heart disease, lowering high homocysteine levels (which may contribute to heart disease), male infertility, diabetes, sleep disorders, depression, mental disorders, weak bones (osteoporosis), swollen tendons, AIDS, inflammatory bowel disease, asthma, allergies, skin disease called vitiligo, preventing cervical and other cancers, and skin infections. Some people use vitamin B12 for amyotrophic lateral Sclerosis (Lou Gehrig’s disease), multiple sclerosis, preventing the eye disease age-related muscular degeneration (AMD), Lyme disease and gum disease. It is also used for ringing in the ears, bleeding, liver and kidney disease, and for protection against the poisons and allergens in tobacco smoke [2].

Milk is an excellent source of vitamin B12. Intake for this vitamin in milk products appears to be highly bioavailable, adequate consumption of milk may aid in the prevention of vitamin B12 deficiency [3].

In Pernicious anemia (PA) (also known as Biermer’s disease and Addisonian anemia), the body does not make enough red blood cells. It is caused by loss of gastric parietal cells, which are responsible, in part, for the secretion of intrinsic factor [a protein essential for subsequent absorption of vitamin B12 in the ileum] [4]. Pernicious anemia accounts for 80% of cases of megaloblastic anemia, due to impaired absorption of vitamin B12. It is believed to be an autoimmune disease [5].

Other causes of vitamin B12 deficiency include

1. Gastric causes: Gastrostomy, gastric resection, atrophic gastritis, H. pylori infection or congenital IF deficiency or abnormality.

2. Inadequate dietary intake of vitamin B12-e.g, a vegan diet.

3. Intestinal causes- e.g., mal-absorption, ileal resection, crotch’s disease affecting the ileum, and any radiotherapy causing irradiation of the ileum.

4. Drugs-e.g., colchicine, neomycin, metformin, anticonvulsants.

5. Long-term use of drugs that affect gastric acid production (e.g., H2 receptor antagonists, proton pump inhibitors) can worsen deficiency because gastric acid is needed to release vitamin B12 bound to proteins in food [6].

The cyanocobalamin has a large molecular weight (M=1355.7 g/mol), but based on clinical studies it can get through the mucous membranes by passive diffusion, which could enable the possible noninvasive applications of the vitamin B12.

Based on its poor bioavailability and good solubility, the B12 belongs to the third class of the Biopharmaceutical Classification System (BCS). It means that it can be successfully applied in a dosage form which assures sufficient time for its membrane penetration.

The applicability of the dosage forms determined by the combination of micro- and the macro structural properties. The commonly used macro structural measurements (determination of the mechanical behavior, dissolution testing) [7].

A wide range of drug delivery systems and associated rate controlling mechanisms were established for controlled release of drugs. Polymers With the wide variety of physicochemical properties play a vital role to tailor the drug release profile. Polymeric drug delivery systems improve bioavailability and therapeutic efficacy of drugs with reduced toxicity. Further it facilitates sustained delivery of drugs and helps in targeted delivery also. B12 drug delivery is feasible in many ways namely intra dermal injection, pulmonary delivery mode and by transdermal and Buccal patches [8].

The use of an effective dosage of vitamin B12 over a period of time can prevent recurring of buccal, nasal, gastrointestinal, anal, and/or vaginal mucosal lesions or injury of any origin, regardless of serum Vitamin B12 level [9].

Vitamin B-12 is called an enzyme co-factor because it’s required for certain enzymes to function. One of these enzymes, methionine synthase, produces an essential amino acid called methionine that helps add a chemical group called a methyl group to more than 100 different compounds, including DNA, RNA and proteins. Your cells use methylation to activate genes, a process critical to hundreds of
Human vitamin-B12 transport mechanism

Vitamin B12 is important for metabolism. Metabolism within the body includes the processes of energy generation and use; including nutrition, digestion, absorption, elimination, respiration, circulation, and temperature regulation.

Humans have a complex process for gastrointestinal absorption of dietary vitamin B12. Vitamin B12 released from food protein is first bound to haptocorrin (salivary vitamin B12-binding protein) in the stomach. After proteolysis of haptocorrin–vitamin B12 complex by pancreatic proteases in the duodenum, the released vitamin B12 binds to intrinsic factor (IF, gastric vitamin B12-binding protein) in the proximal ileum. The IF–vitamin B12 complex can enter mucosal cells in the distal ileum by receptor-mediated endocytosis.

Bioavailability of dietary vitamin B12 is significantly dependent on this gastrointestinal absorption. Recent evidence that suggests vitamin B12 is associated with risk reduction for some chronic diseases and birth defects [11].

The treatment of PA varies from country to country and from area to area. A permanent cure for PA is lacking, although repletion of B12 should be expected to result in a cessation of anemia-related symptoms, a halt in neurological deterioration, and (in cases where neurological problems are not advanced) neurological recovery and a complete and permanent remission of all symptoms, as long as B12 is supplemented. Repletion of B12 can be accomplished in a variety of ways [12].

There appears to be some confusion among practitioners of natural medicine about whether oral, intramuscular, buccal patches administration or any other method is preferable for patients requiring vitamin B12 therapy for the treatment of pernicious anemia [13].

Researching supplements is NOT easy because most scientific research seems inconclusive and the FDA does not regulate OTC vitamins much. It’s even harder to try to determine whether vitamins B12, sublingual (dissolving) tablets, or patches or oral tablets work better or worse.

Oral dosage form of vitamin B12

The absorption of ordinary amounts of vitamin B12 from the gastrointestinal tract is normally dependent on the presence of the intrinsic factor of Castle in the gastric secretions. A lack of intrinsic factor results in deficient absorption of vitamin B12 and the clinical picture of pernicious anemia. In the treatment of this condition, it has been necessary either to administer vitamin B12 parenterally or to add intrinsic factor to the vitamin B12 given by mouth to ensure proper absorption [13].

The oral treatment of Pernicious Anemia with CN-Cbl and OH-Cbl provides cells with a source of cobalamins that can be internalized to form active coenzyme forms. A daily intake of 2.4 µg of Vitamin B12 has been proven to be sufficient in replenishing the normal amount of B12 lost through metabolism. However, due to the lack of IF in patients with PA, the intrinsic-factor-mediated absorption is disrupted and the efficiency by which Cbl is absorbed by the ileum is reduced to 1-5% via passive diffusion. The results of an open study of 10 patients with pernicious anemia demonstrated that an oral mega dose of 1000 µg/day of CN-Cbl for 3 months increased the serum cobalamin levels by an average 117.4 µg/ml as well improve the clinical abnormalities in 30% of the patients. The recommendation of a daily oral mega dose of CN-Cbl for life has not been made a definitive treatment for PA; however, relative to current parenteral treatments, oral treatments are less time consuming, lower in cost, and more convenient for the patient [14].

Study was conducted to compare the pharmacokinetics and tolerability of 2 oral formulations of Cyanocobalamin—a marketed Cyanocobalamin tablet (immediate-release B12 5 mg) and Cyanocobalamin formulated with a proprietary carrier, sodium N-[8-(2-hydroxybenzoyl) amino]caprylate (SNAC)–to establish the feasibility of using an absorption enhancer with B12 to improve uptake of the vitamin. This was the first clinical study conducted with the Cyanocobalamin/SNAC co-formulation. The pharmacokinetics properties of vitamin B12 were characterized by non-compartmental analysis. Vitamin B12 absolute bioavailability estimates were calculated between the oral and IV treatments using non-baseline-adjusted vitamin B12 concentrations as well as baseline-adjusted vitamin B12 concentrations, with or without body weight adjustments [15].

Tolerability was evaluated through review or monitoring of medical history, physical examination findings, concomitant medications, vital signs, laboratory tests (hematology, serum chemistry, and urinalysis values), electrocardiography, adverse events, and serious adverse events. Both oral formulations and commercial 1-mg cyanocobalamin IV were well tolerated [15].

A clinical trial of oral treatment of pernicious anemia was carried out with a preparation containing a combination of vitamin B12 and intrinsic factor. In four out of five previously untreated patients there was a satisfactory response; in the fifth the treatment was ineffective, but the patient subsequently responded to parenteral vitamin B12. In 12 patients previously treated with vitamin B12 by injection and transferred to maintenance treatment with the oral preparation the hemoglobin and red-cell count showed over one year a significant fall. In a further patient on oral maintenance therapy, features of subcutaneous combined degeneration developed. It is concluded that at present oral therapy is not as reliable for the treatment of pernicious anemia [16].

Buccal patches based delivery of vitamin B12

Owing to the ease of the administration, the oral cavity is an attractive site for the delivery of drugs. Through this route, it is possible to realize mucosal (local effect) and Tran’s mucosal (systemic effect) drug administration. In the first case, the aim is to achieve specific Site Release of drug on the mucosa, whereas the second involves drug absorption through the mucosal barrier to reach the systemic circulation [17].

Buccal films are preferable over adhesive tablets in terms of flexibility and thinness thus being less obtrusive and more acceptable to the patient [18].

Drug release from Muco adhesive matrices is known to be the complex interaction between diffusion, swelling and erosion mechanisms [6].

In the development buccal drug delivery systems, Muco-adhesion is a key element. Muco-adhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucoses [20]. The actual absorption of B-12 into the body is a real problem with oral tablet-based supplements. A study carried out at the Department of Pharmacology at the University of Dublin found that delivering a dose of nutrients/medication using buccal patches rather than with oral tablets that are swallowed resulted in a greater than 95% absorption rate of the patches’ nutrient formula directly into the bloodstream. The study also found that with Tablets, patients absorbed as little as 5% of the Tabs’ stated nutrient dose.
Based on its poor bioavailability and good solubility, the B₁₂ belongs to the third class of the Biopharmaceutical Classification System (BCS). It means that it can be successfully applied in a dosage form which assures sufficient time for its membrane penetration the bypass of first pass effect and the avoidance of pre-systemic elimination within the GIT. By the use bio adhesive polymeric systems the proper adhesively to the mucosa can be assured, thus the absorption of the drug through the membrane will be supported. For buccal administration, vitamin B₁₂ was applied daily to the floor of the mouth in the sulcus between the alveolar margin and the cheeks [6, 19].

**Intra-muscular based delivery of vitamin B₁₂**

According to nutrition issues in gastroenterology the quantitative dose of Vitamin B₁₂ required in pernicious anemia is less in intramuscular than in oral dosage form Oral (synthetic) 1000 µg/day for 1–4 weeks, Parenteral 1000 µg/day for 1 week) [20, 21].

It passes first pass metabolism and the absorption is faster in intrinsic factor deficient person Low dose is required when compared to oral dose. Administration of Vitamin B₁₂ by intramuscular injection has certain drawbacks, it is inconvenient for administering as professional practitioners are required self-administration is difficult economic wise it is quite expensive and dosing is painful, it has low retention time compared to Buccal formulation [22].

While serious adverse reactions are rare, injections can be dangerous in anti-coagulated patient a sensitivity history should be obtained from the patient prior to administration of Vitamin B₁₂. An intradermal test dose is recommended before Vitamin B₁₂ is administered to patients who may be sensitive to Cobalamin [23].

**Comparison between various formulations of Vitamin B₁₂**

**Cost**

Suggested retail prices indicate that the cost of oral Vitamin B₁₂ therapy at a dose of one Also high compared to buccal and parenteral dosage form buccal patches are cheap compared to other two formulations.1000 µg tablet daily is approximately equivalent to the cost of taking 500 mg of calcium and 1000 IU of Vitamin D [24]. As dose of the drug given by oral is high, cost is also high compared to other two formulations.

**Safety**

Vitamin B₁₂ injections can be dangerous in anti-coagulated patients Hypo-kalma and cardiac arrest has been reported when megaloblastic anemia is treated intensively. Pain full and require assistance. Oral administration is safe compared to intramuscular injection but requires 1000µg-2000 µg per day. buccal patches are convenient, safe and easy to insert and low drug is required prolonged effect can be obtained.

**CONCLUSION**

The Intramuscular route is painful and requires medical assistance in dosing and it is quite expensive, retention time is low as it absorbs faster (fast reaction). The oral intake of B₁₂ requires a large amount of drug because The GI tract is a lipid based membrane and being more hydrophobic in nature is less suitable for absorption of hydrophilic drug vitamin B₁₂. From above information buccal route is more reliable in treatment of pernicious anemia, it enhances the bio availability of vitamin B₁₂, and this route of drug delivery is of special advantages, including the bypass of first pass effect and the avoidance of pre systemic elimination within the GIT.

**CONFLICT OF INTERESTS**

Declare None

---

**REFERENCES**