CASE REPORT

Megaloblastic Anaemia: Response To Amples A And B (Folic Acid, Vitamin B 12 (Cyanocobalamin), Niacin And Vitamin C) - A Case Report

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ABSTRACT

Background: *Megaloblastic anaemia is prevalent in our society and patients are diagnosed late.*

Method: *Case Report of a patient with megaloblastic anaemia and discussion of relevant literature.*

Results: *A 50year old Nigerian trader with recurrent chronic anaemia and repeated blood transfusions (Eight units in 10days) was finally diagnosed to have megaloblastic anaemia. He was commenced on intramuscular, Ample A and Ample B (folic acid 0.7mg, vitamin B12 (Cyanocobalamin) 2500g, niacin 12mg and vitamin C 150mg) on alternate days (6 doses) then weekly as maintenance until haematocrit returned to normal. Response was dramatic; haemoglobin was 6.4g/dl before, 7.9g/dl after the second dose and 11.5g/dl after the 6th dose of the drug. The corrected retic was 2.0% before, 4.6% 72hrs after and 8.4% after the 6th dose .The MCV decreased from 105fl before to 79fl after the 6th dose of the drug. His packed cell volume has remained above 35% after completing the 6th dose and during maintenance therapy.*

Conclusion: *The combination of cyanocobalamin, folic acid, niacin, and vitamin C, in Amples A and B is complementary. Treatment with amples A and B is effective and affordable in the management of megaloblastic anaemia.*

KEY WORDS: *Megaloblastic anaemia; Vitamin B12; Cyanocobalamin; Folic acid; Niacinamide; Vitamin C; Hydroxocobalamin.*

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INTRODUCTION

The term Megaloblast was coined in 1880 by Paul Erhlich, the father of present day chemotherapy[1]. Megaloblastic anaemia can be defined as a group of disorders characterized by the presence of distinctive morphological appearance of the developing red cells in the bone marrow. The aetiology is mainly deficiency of vitamin B12 (cobalamin) and folic acid, resulting in defects in DNA synthesis.

The prevalence of vitamin B12 deficiency has ranged from 3% to 29%[2]. Vitamin B12 is found in Animal products mainly (liver and kidney have the highest sources of vitamin B12 up to 100g/100g). It is not found in plant kingdom except when contaminated by bacteria[3]. The latest recommended dietary allowance (RDA) for adults is 2.4 g/day[4] and stores can last for 3 to 4 years.

There are four important clinical forms of cobalamin in animal cell metabolism viz: cyanocobalamin, hydroxocobalamin, adenosylcobalamin and methylcobalamin. Methylcobalamin and 5-deoxyademosyl cobalamin are the forms of vitamin B12 used in the body[3]. cyanocobalamin and Hydroxocobalamin are readily converted to adenosylcobalamin and methylcobalamin.

Cyanocobalamin and hydroxocobalamin are the most commercially available forms of vitamin B12. Although the amount of cyanide is considered toxicologically insignificant, humans must remove and detoxify the cyanide molecule and then convert the cobalamin to metabolically active coenzyme forms[5]. Cyanocobalamin is available and used in the United States and hydroxocobalamin is available and preferred in Europe[6].

Usually in our environment differentiating folic acid deficiency from cobalamin deficiency is difficult and thus replacement for both is usually the therapy for a diagnosed megaloblastic anaemia.

Amples A and B unlike other drugs (containing only cyanocobalamin for treatment of cobalamin deficiency) has other vitamins added to cyanocobalamin viz; folic acid 0.7mg, niacinamide 12mg and vitamin C 150mg. Niacinamide also called niacin, nicotinic acid and referred to as vitamin B3 is required for cell respiration, and helps in the release of energy and metabolism of carbohydrate, fats, proteins, proper circulation and healthy skin, functioning of the nervous system and normal secretion of bile and stomach fluids. Deficiency may cause pellagra the classical niacin deficiency disease characterized by bilateral dermatitis, diarrhoea and dementia. It has been noted that niacin is best taken with other vitamin B groups and vitamin C.

Vitamin C (ascorbic acid), a reducing agent, is necessary to maintain the enzyme prolyl-hydroxylase in an active form most likely by keeping its iron atom in a reduced state. This enzyme acts on

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proline and lysine in procollagen and uses vitamin C as a cofactor. A deficiency of vitamin C results in breakdown of the protein collagen needed for connective tissue, bones and dentin. Lack of vitamin C may lead to haemorrhage because capillaries lack collagen. This haemorrhage is worsened in a Megaloblastic anaemia patient with thrombocytopaenia. Vitamin C has been found also to increase the absorption of iron from the gastrointestinal tract by increasing the acidity in gut. This paper reports a patient with megaloblastic anaemia who had a dramatic response with Amples A and B.

CASE REPORT

A 50-year old male Nigerian trader, M. R., who presented to the Accident and Emergency Centre of University of Benin Teaching Hospital (UBTH) with a 3-week history of generalized weakness. The weakness was gradual over a period of one year but became worse 3 weeks before presentation. He had been to several private hospitals where he was placed on haematinics (iron, folic acid, vitamin C) and transfused with 8 units of blood over the last 10 days before presentation.

He was said to have collapsed with loss of consciousness for a period of 10minutes on the day of presentation. He was not a known diabetic or hypertensive patient. There was no history of bleeding disorders, pruritus, cough or fever. He is widowed with two children but lives alone and not a vegan. Physical examination, at the time of presentation, revealed a middle-aged man who was conscious, not in any obvious respiratory distress, chronically ill-looking, warm to touch, pale, tinge of jaundice, not dehydrated, nil pedal oedema, nil peripheral lymphadenopathy. The chest was clear clinically, pulse rate was 118b/min regular with normal volume, blood pressure was 150/90mmHg (supine), and heart sounds were I and II only. The abdomen was full, soft with splenomegaly of 6cm below the left mid -subcostal margin, firm and non-tender. Other abdominal organs were not palpable. There were no significant neurological signs except mild numbness and shooting pains in both lower limbs, worse at the feet.

Investigations were ordered and results showed a packed cell volume (PCV) or haematocrit of 21% (patient had 2 units of blood same day before he was referred from a private hospital). Haemoglobin (Hb) was 6.4g/dl, mean corpuscular vol (MCV) was 105 fl, corrected retic was 2.0%, white blood cell count (WBC) was 8.1X10^9/L, Platelet count was 230 X10^9/L.A peripheral blood film done showed a dimorphic picture (most likely due to recent blood transfusion). Also there were hypersegmented neutrophils. Bone marrow aspiration showed numerous Megaloblasts with moderate number of dying cells (ineffective erythropoiesis) and some giant metamyelocytes suggestive of megaloblastic anaemia. Confirmatory test for megaloblastic anaemia with the use of urine methylmalonic acid assay could not be carried out due to some constrains. Electrolytes, urea and creatinine were within normal limits. Coomb's test (direct and indirect) was negative, chest radiograph was normal, no ova and parasite in stool and retroviral screening was negative.

However, since patient had had about 8 units of blood containing iron and had been on folic acid for several months without clinical and laboratory response, the use of cobalamin replacement was considered. The patient was placed on intramuscular Amples A and B (Vitamin B12 (Cyanocobalamin) 2500g, folic acid 0.7mg, Niacinamide 12mg and vitamin C 150mg) on alternate days (6 doses) then weekly as maintenance. A follow up was done 72 hours after commencement of therapy with Amples A and B. After 2 doses, investigations showed a haematocrit of 25%, Haemoglobin of 7.9g/dl, white blood cell count of 7.8 X10^9/L, Platelet count of 220 X10^9/L, MCV was 85fl, corrected retic of 4.6 electrolytes and urea were normal and splenomegaly had reduced to 3cm. At the end of the 6th dose, haematocrit was 36%, Hb was 11.5g/dl, white blood cell count 7.6 X10^9/L, Platelet count of 225 X10^9/L, MCV was 79fl, corrected retic was 8.4%, electrolytes and urea were normal. Splenomegaly totally disappeared and the bone marrow erythroid cells returned to normal (Table I). The patient was discharged home after completing the 6th dose and kept on maintenance. His haematocrit has remained above 35% after discharge and one month of maintenance. The patient has not been transfused since commencement of Amples A and B.

Table I. Parameters: Pre and Post Therapy with Amples A and B.

	Hb (g/dl)	WBC (X10 ^{9}/L)	PLT (X10 ^{9}/L)	MC V(fl)	CR(%) Corrected retic	S(cm) Splenomegaly Below costal margin
Pre - therapy	6.4	8.1	230	105	2.0	6
3-days post - therapy	7.9	7.8	220	85	4.6	3
14days post - the rapy	11.5	7.6	225	79	8.4	0

DISCUSSION

Megaloblastic anaemia is prevalent in Nigeria and most of the time the aetiology of Cobalamin or folic acid deficiency is not known. However in this patient, a nutritional cause cannot be excluded because there is a history of poverty and he stays alone without enough money to eat good source (animal products) of vitamin B12.

The table of results monitoring response to Amples A and B shows that the haemoglobin level in this patient increased from 6.4g/dl (before commencement of Amples A and B) to 11.5g/dl 14 days after commencement of Amples A and B. The haemoglobin remained at 11.5g/dl at the end of 30 days when patient was on maintenance dose every two weeks. Also the results show that the mean Cell Volume (MCV) reduced from 105fl to 79fl while the corrected retic increased from 2.0% to 8.4% after 6doses of Amples A and B. The corrected retic at presentation was 2.0% and the Haemoglobin of 6.4g/dl, this shows inappropriate response of the marrow to the level of anaemia, and this therefore makes the possibility of a haemolytic anaemia less likely.

These parameters showed a good and dramatic response to Amples A and B injections. The patient may have gradually depleted his stores of cobalamin over years and became worse 3 weeks before presentation because the stores can last for 3-4 years without adequate intake of cobalamin. This patient has been to several hospitals, was on oral iron, folic acid, vitamin C, and has had 8 units of blood, each containing about 250mg of iron. The rise in haemoglobin (Hb) of the patient cannot be explained by the several blood transfusion because after three to four units of blood the patients Hb would have risen above 6.4g/dl, but after eight units of blood, the Hb was still 6.4g/dl at presentation. The patient who has been on folic acid for two months most likely lacked cobalamin, which is one of the major causes of megaloblsastic anaemia as shown by response to the therapeutic trials of amples A and B. The use of folic acid in this patient with cobalamin deficiency may be contributory with iron replacements for the transient increase in Hb observed during the blood transfusion but was not sustained. However it has been documented that patients with neurological complications of cobalamin deficiency, will be worsened by folic acid therapy alone. Therefore it is advised, to commence cobalamin and folic acid at the same time when megaloblastic anaemia is confirmed by bone marrow cytology studies and there are no facilities to distinguish folic from cobalamin deficiency . Amples A and B have provided the replacement of cobalamin as 2500g of cyanocobalamin to replace the stores with 6 doses before maintenance.

There are two main commercial sources of Cobalamin; viz: hydroxocobalamin Chloride and cyanocobalamin.

Table II. Comparing Hydroxocobalamin with Cyanocobalamin (amples A and B)

	Hydroxocobalamin	Cyanocobalamin(amples A and B)
Dosage	1000µg alt days	2500µg alt days
Duration for stores	6 doses	6 doses
Maintenance	Every 1 to 3 months	Every one to two weeks
Pharmakokinetics	* Retained more * Less absorbed from i.m. site	* Rapidly absorbed from i.m site * Peak plasma levels in 1 hour
Response	* Marrow change within 12 - 72hours * Reticulocytosis starts 3-5days and Peaks 4 to 10 days * Hb normal 1 to 2 months	* Marrow change within 72 hours * Reticulocytosis starts 3-5days and Peaks 4 to 10 days * Hb normal 1 to 2 months
Drug interactions	Impaired by chloramphenicol etc	Rare
Adverse reactions	Hypersensitivity (itching, exanthema and rarely anaphylaxis * Antibodies to hydroxocobalamin Transcobalamin II complex	*Little or unknown *Rarely anaphylaxis
Other vitamins	Nil	Vitamin C, niacin, Folic acid
Cost	* N6,000 to replace stores	* N600 to replace stores

Hydroxocobalamin has been shown to be retained more in the body than cyanocobalamin.Thus maintenance with hydroxocobalamin is one to three times monthly while that of cyanocobalamin is more frequent. This has made some centres to replace cyanocobalamin with hydroxocobalamin. Also pharmakokinetics have shown that hydroxocobalamin has a higher and more prolonged serum level of vitamin B12 than cyanocobalamin when given intramuscularly in the same dosage. Cyanocobalamin is rapidly absorbed from intramuscular and subcutaneous sites than hydroxocobalamin. Peak plasma levels are obtained one hour after injection of cyanocobalamin and drug interaction of cyanocobalamin is rare while hydroxocobalamin's therapeutic response is impaired by interaction with chloramphenicol etc. Various adverse reactions have occasionally been reported but none of these in recent years can be classified as either certainly or probably due to cyanocobalamin therapy but adverse reaction to

hydroxocobalamin include hypersensitivity (itching, exanthema and rarely anaphylaxis); Antibodies to hydroxocobalmin Transcobalamin II complex may develop during hydroxocobalamin therapy.

Maintenance therapy is very important to avoid relapse. In a study it was found that one or more episodes of recurrent megaloblastic anaemia occurred in 36 (10.8%) of 333 patients with pernicious anaemia following interruption of therapy. Treatment had most commonly been discontinued by patients because they felt well or by physicians due to error. Thirty five episodes of recurrent cobalamin deficiency were analysed by some authors in details and it was discovered that the interval before relapse was 64.5 months (range 21 to 123 months)[7].

This response to cyanocobalamin by this patient is similar to documented response to hydroxocobalamin in the literature. Patients on hydroxocobalamin demonstrate marrow change within 12 hours from megaloblastic to normoblastic, a process that is complete in 2 to 3 days. Reticulocytosis begins on day 3 to 5 and peaks on day 4 to 10. The blood haemoglobin concentration becomes normal within 1 to 2 months[8]. In this case study, within 72hrs post therapy, the haematocrit had risen from 21% to 25% with a reduction of MCV from 105fl to 85fl and the corrected retic from 2.0 to 4.6. On the 14th day of commencing Eldervit-12, the Haematocrit had risen to 36% (Haemoglobin of 11.5gldl) MCV of 79fl and a corrected retic of 8.4. Although a bone marrow cytology was not done within 12 hrs, on day 14 of commencing Amples A and B, a repeat marrow study showed a change from magaloblastic to normablastic picture.

The reason for the use of Amples A and B was because it is affordable and effective. One ample (dose) of hydroxocobalamin will cost N1, 000.00 (one thousand naira). Thus 6 doses will cost a total of N6, 000.00 (six thousand naira) to replace the stores while 6 doses of Eldervit-12 will cost the patient N600.00 (six hundred naira) only.

Although this patient may have benefited from the cyanocobalamin component of Amples A and B, it is obvious that the combination of niacin, vitamin C and folic acid is complementary. This is because in most patients with megaloblastic anaemia, specific diagnosis of folic acid or Cobalamin deficiency may be difficult, so a combination of folic acid and vitamin B12 is therapy of choice. Patients with megaloblastic anaemia may also have iron deficiency as combined deficiency, therefore benefiting from vitamin C, which increases the absorption of iron from the gut. Also vitamin C prevents the bleeding associated with thrombocytopaenia, small sized platelets and functionally abnormal platelets in some megaloblastic anaemia patients.

Finally, niacin has been shown to be more effective when combined with other vitamin B groups and vitamin C.

The patient in this case study presented with complaints of mild numbness and shooting pains in the lower limbs (Lhermitts sign) which subsided during therapy but did not disappear completely. There are several other complications of megaloblastic anaemia. Neuropsychiatric complications can present as subacute combined degeneration of the spinal cord. The psychiatric mask and the lack of clinical anaemia in some patient (25% of cases) with cobalamin deficiency is a chief obstacle to early diagnosis[9]. Most Haematologist use morphological picture (bone marrow aspiration) to make a diagnosis of megaloblastic anaemia although it has been shown by several authors that methylmalonic acid levels in 24 hours urine samples is a more reliable indicator of cobalamin deficiency than the use of serum cobalamin levels or serum methylmalomic acid levels[10].

CONCLUSION

Megaloblastic anaemia is prevalent in our society and patients are diagnosed very late after they patients have been transfused with several units of blood with its attendant hazards. Most of the patients present with anaemia but about 25% of patients with neuropsychiatry complications may not present with anaemia.

Response to cobalamin therapy is very dramatic. Since there is little or no known adverse effect even with the administration of up to 10,000 times the human requirements[5], some authors have advocated the routine use of vitamin B12 (as prophylaxis) to ameliorate mental illness especially dementia in the elderly even when vitamin B12 levels appear normal.

Amples A and B has been found to be very effective in the management of megaloblastic anaemia. Although hydroxocobalamin is retained longer in the body than cyanocobalamin, the drug interactions, adverse side effects and the cost of hydroxocobalamin makes the use of cyanocobalamin a drug to be considered in the management of megaloblastic anaemia in our society, as obtains in the United States[6].

In this patient diagnosis as in common practice was based on clinical history, bone marrow cytology

and response to therapy (therapeutic trials), therefore future studies with confirmatory diagnosis is recommended. Finally, although the combination of folic acid, vitamin C and niacin in Amples A and B is complementary in the management of megaloblastic anaemia especially in combined deficiencies, a selective trial with only cobalamin supplement is recommended for future studies.

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