

Parenteral Cyanocobalamin Induced Arthralgia: A Case Report

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ABSTRACT

Cyanocobalamin is a presently coenzyme mainly involved in reactions leading to synthesis of Nucleic Acids and of that of methionine from homocysteine. On the other hand hematological neurological and epithelial clinical manifestations observed during Vitamin B₁₂ deficiency may lead to Pernicious anemia. Pernicious anemia is a megaloblastic anemia which leads to abnormal erythrocyte nuclear maturation and leading to ultimate effect of loss of adequate stores of the Vitamin B₁₂. Arthralgia induced after / following cobalamin administration is rarely. Despite of that various drugs are known to cause musculoskeletal adverse events such as arthralgia, myalgia and serum sickness. We present a Case of a 54 Year Old Male, with chief complaint of fever, pallor skin, shortness of breath and tiredness. On the fifth day, patient develops cyanocobalamin induced arthralgia and main treatment of the drug induced arthralgia is the discontinuation of the responsible drug. However patients can be managed with one active

form of Vitamin B₁₂ which is methyl cobalamin that has excellent beneficial therapeutic management for Joint Pain. In this case report a rare adverse event of Vitamin B₁₂ Injection inducing arthralgia is reported.

Key words: DIA, Vitamin B₁₂, Arthralgia, Naranjo Probability Scale, Adverse Drug Reaction.

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INTRODUCTION

Cyanocobalamin is commonly used in the management of megaloblastic anemia which is mostly caused by deficiency of Vitamin B¹².¹ Cyanocobalamin is a presently coenzyme mainly involved in reactions leading to synthesis of Nucleic Acid and of that of methionine from homocysteine.² Although on the other hand hematological neurological and epithelial clinical manifestations observed during Vitamin B₁₂ deficiency may lead to Pernicious anemia. Pernicious anemia is a megaloblastic anemia which lead to abnormal erythrocyte nuclear maturation and leading to ultimate effect of loss of adequate stores of the Vitamin B₁₂.³ However cobalamin deficiency may occur due to bacterial overgrowth in intestine causing intestinal malabsorption of the Vitamin B₁₂. Despite of that it remains in use for megaloblastic anemia resulting from vitamin B₁₂ deficiency due to lack of intrinsic factor, where by impaired intrinsic factor production may occur in adults due to autoimmune destruction of parietal cells which secrete intrinsic factor in the intestine, However several conditions other than impaired Intrinsic Factor production may cause a megaloblastic anemia such as deficiency of folic acid, altered pH in the small intestine and lack of absorption of Vitamin B₁₂ complexes in the terminal ileum.⁴

The risk of arthralgia induced after cobalamin administration is rarely occurred various drugs are known to cause musculoskeletal symptoms such as arthralgia's, myalgia's and serum sickness. The mostly commonly recognized drugs that can cause musculoskeletal symptoms are hydralazine, minocycline, Statins and dipeptidyl peptidase -4 inhibitors.⁵ To our knowledge no literatures have been reported for parenteral cyanocobalamin administration induced arthralgia.

Cyanocobalamin is hydroxylated active form of Vitamin B₁₂ and large molecule in which trivalent cobalt ion is coordinated in the four rings which is essential for growth cell reproduction hematopoiesis and nucleoprotein and myelin synthesis and involves in Coenzyme metabolic

functions include protein synthesis and carbohydrate metabolism where by plays a major role in cell replication including hematopoiesis. Cyanocobalamin is the most stable and widely used form of Vitamin B₁₂ and has hematopoietic activity apparently identical to that of the anti-anaemia factor in purified liver extract.⁶ Although Parenteral intramuscular administration of Vitamin B₁₂ completely reverses megaloblastic anaemia and gastro intestinal symptoms of Vitamin B₁₂ deficiency.⁷

This case report elaborate rarely occurrences of Vitamin B₁₂ following parenteral administration inducing arthralgia an appropriate intervention such as discontinuation of the responsible drug is the mainstay in reduction of chances for developing Adverse drug Reaction.

CASE DESCRIPTION

A -54- Year Old Male was admitted to Male Medical Ward at Government Headquarters Hospital, Ooty with chief complaint of fever, pallor skin, shortness of breath and tiredness. The patient past medical history was unremarkable and he revealed that of not knowing his past medication history. According to his social history findings patient was found to be alcoholic for past twenty-three years and he denied of smoking. On clinical examination patient vital signs were unremarkable. The laboratory investigations which were found abnormal were hemoglobin, Complete blood count which included slightly elevation of Mean cell volume and elevated alkaline phosphate liver enzyme (Table 1).

According to signs and symptoms patient was diagnosed with severe megaloblastic anemia On the first day patient was administered with Injection Paracetamol 300mg I.Mq8Hr, Injection Ranitidine 50mg I.Vq12Hr, Tablet Domperidone 10mg B.D Tablet Vitamin B complex

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O.D and On the Second day patient was administered with Blood Transfusion 350ml IM as well with Tablet Albendazole P.O 400mg.

On the third day the patient was prescribed with Injection cyanocobalamin 200mcg, Tablet Multivitamin B.D, Tablet Ranitidine 150mg B.D. On the Fourth Day Patient had developed an Adverse drug Reaction (ADR) of drug induced arthralgia which was complaint of the patient and eventually recommended to discontinue administration of Vitamin B₁₂ injection which was highly suspected and patient was administered with Paracetamol Injection 300mg I.M for management of arthralgia and was continued with blood transfusion therapy as well. On the Fifth day patient continued with the same medication, However Parenteral administration of cyanocobalamin was withdrawn and Recommended to Clinician to switch from parenteral therapy to oral therapy into our patient. Certainty his joints pain was subsided and Patient was discharged.

DISCUSSION

Drug-induced arthralgia (DIA) is defined as the acute or subacute manifestation of arthralgia, drug-induced arthralgia can occur as a side effect of a large number of prescribed medications that likely tend to occur and causing joints pain. It is important that to recognize initially when a patient's has rheumatic complaints due to prescribed medications.⁸ Symptoms which include muscle weakness, myalgia, creatine kinase elevation and myoglobinuria that can occur in patients without any rheumatic disorders when they are exposed to certain drugs.⁹ Cyanocobalamin drug induced joint pain disorder is rare reported,

However there are few literatures which have been reported of the drug induced arthralgia's and majority of this drugs exert pharmacological actions although some of the medications tend to harm other organs of the body which may influence occurrences of side effects due to drugs and leading to different part of body system to be affected. Drug-induced arthralgia (DIA) which have been found to occur with following medications such as Fluoroquinolones, Statins, Voriconazole Tumor necrosis factor- α inhibitors, Leflunomide, Zidovudine, Chloroquine and Hydroxychloroquine. Although as per Literature till date nothing has been reported of Cyanocobalamin induced arthralgia, Parenteral Vitamin B₁₂ administration is widely used for treatment of Megaloblastic anemia and Vitamin B₁₂ deficiency. However remains to be observed whether more cases of Cyanocobalamin induced arthralgia will occur and to be reported.

A review of the literature study that was conducted on effect of combined diclofenac and B vitamins (Thiamine, Pyridoxine and Cyanocobalamin) for Low back Pain management reported that cyanocobalamin as monotherapy delivered by Intramuscular Route has been assessed in patients with chronic back pain, Therefore we correlates our findings that this Adverse effect is Paradoxical since Vitamin B₁₂ works as an analgesic co-adjuvant.¹⁰ Although Drug induced arthralgia DIA commonly can result in necrosis, cytoplasmic membrane changes and increasing in mitochondria dysfunction, Symptoms that occur with drug-induced

Table 1: Clinical laboratory Test.

Test Parameter	Observed Value	Reference Range
Hemoglobin	5.2g/dL	14g/ dL -18g/dL
White blood cells	5.5 \times 5 ³ cells/mm ³	3.2-9.8 \times 2 ³ cells/mm ³
Hematocrit	38.6%	33 -43%
Mean cell volume	108.4fL	76 -100fL
Mean cell hemoglobin	36.4pg/cell	27 -33pg/cell
Mean cell hemoglobin concentration	33.5g/dL	33 -37g/dL
Fasting Blood sugar	85mg/dL	< 100mg/dL
Blood urea	26mg/dL	20 -40mg/dL
Serum creatinine	1.0mg/dL	0.6 -1.2mg/dL
Blood urea nitrogen	10m g/dL	8 -18mg/dL
Aspartate aminotransferase	26U/L	0 -35U/L
Alanine aminotransferase	17U/L	0 -35U/L
Alkaline phosphates	155U/L	30 -120U/L
Bilirubin Total	1.7mg/dL	0.1 -1mg/dL
Bilirubin Direct	0.7mg/dL	0 -0.2mg/dL
Bilirubin Indirect	1.0mg/dL	0.1 -0.8mg/dL
Urine sugar	Nil	Nil
Urine albumin	Nil	Nil
Platelet Count	64 \times 10 ³ cell/mm ³	130-400 \times 10 ³ cell/mm ³

Hemoglobin (Hb); Hematocrit (Hct); Mean cell volume (MCV); Mean cell hemoglobin (MCH) Mean cell hemoglobin concentration (MCHC); Blood urea (BU); Blood urea nitrogen(BUN) Serum creatinine (Sr.cr); Aspartate aminotransferase (SGOT); Alanine aminotransferase (SGPT) Alkaline phosphates (ALP)

Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous <i>conclusive</i> reports on this reaction?	+1	0	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a <i>specific</i> antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
TOTAL SCORE				+6

Scoring for Naranjo algorithm: >9 = definite ADR; 5-8 = probable ADR; 1-4 = possible ADR; 0 = doubtful ADR.

Modified from: Naranjo CA *et al.* A method for estimating the probability of adverse drug

arthralgia such as articular multiple joints pain,¹¹ fatigue, myalgia, elevated creatinine kinase are usually not reported especially following parenteral drug administration. However timing of the drug initiation for drug induced arthralgia is a variable when left untreated and which can range from the onset of administration of a drug to several months.¹² Our Patient had complaint of arthralgia on the third day after the administration of cyanocobalamin injection 200mcg where by suspected drug was discontinued and patient was managed with paracetamol 500mg three times a day for the management of joints pain, eventually we suggested to stop the use of parenteral Vitamin B 12. Interestingly joint pain was less severe when drug was switched from parenteral administration (IM) to per oral therapy (P.O) which was found to have less causative effect of inducing arthralgia. In this case event of parenteral cyanocobalamin administration inducing arthralgia to our patient according to Naranjo ADR probability scale showed that adverse drug reaction was Probable with the average score of (+6),¹³ which showed an association of cyanocobalamin inducing arthralgia and suspected drug was withheld.

CONCLUSION

Parenteral administration (IM) of cyanocobalamin inducing arthralgia is rare, appropriately interventions such as discontinuation of medication or to switch from parenteral route to oral route will greatly added an advantage of reducing risk of drug inducing arthralgia. However Patients can be managed with one active form of Vitamin B¹² which is methyl cobalamin that has excellent beneficial therapeutic management for Joint Pain.

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CONFLICT OF INTEREST

The authors declare no conflict of Interest.

ABBREVIATIONS

DIA: Drug-induced arthralgia; **ADR:** Adverse drug Reaction; **IM:** Intramuscular; **PO:** Per Oral.

REFERENCES

1. Wang YH, Yan F, Zhang WB. An investigation of Vitamin B₁₂ deficiency in elderly inpatients in neurology department. *Neurosci Bull.* 2009;25(4):209-15.
2. Carlos AC, Mauricio ON. B Vitamins in the nervous system, Current Knowledge of biochemical modes of action and synergies of thiamine pyridoxine and cobalamin. *CNS Neurosci Ther.* 2020;26(1):5-13.
3. Andrés E, Serraj K, Zhu J, Vermorken AJ. The pathophysiology of elevated Vitamin B₁₂ in clinical practice. *Intel Journal of Med.* 2013;106(6):505-15.
4. Toh BH, Hoffman R, JrBenz EJ, Silberstein LE, Heslop HE, Weitz JI, et al. Pathophysiology and laboratory diagnosis of pernicious anemia. *Immunol Res.* 2017;65(1):326-30.
5. Bannwarth B. Drug-induced musculoskeletal disorders. *Drug Saf.* 2007;30(1):27-46.
6. Leishear K, Ferrucci L, Lauretani F. Vitamin B₁₂ and homocysteine levels and 6-year change in peripheral nerve function and neurological signs. *J Gerontol A Biol Sci Med Sci.* 2012;67(5):537-43.
7. Carmel R. How I treat cobalamin Vitamin B₁₂ deficiency. *Blood.* 2008;112(6):2214-21.
8. Hart F. Drug induced arthritis and arthralgia. *Drugs J.* 1984;28(4):347-54.
9. Dalakas M. Toxic and Drug-induced myopathies. *J Neur Psychiatry.* 2009;80(8):832-8.
10. Calderon-Ospina CA, Nava-Mesa MO, Arbeláez ACE. Effect of combined Diclofenac and B vitamins (thiamine, pyridoxine and cyanocobalamin) for low back pain management: Systematic review and meta-analysis. *Pain Med.* 2020;21(4):766-81.
11. Kuncil W. Agents and mechanisms of toxic myopathy. *Curr Opin Neurol.* 2009;22(5):506-15.
12. Adwan H. An update on drug-induced arthritis. *Rheumat Int.* 2016;36(8):1089-97.
13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30(2):239-45.

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