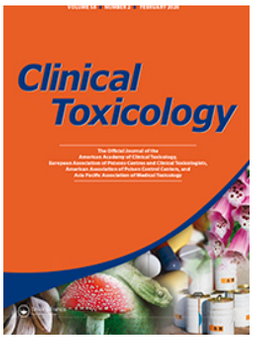

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SHORT COMMUNICATION

Toxicity induced by multiple high doses of vitamin B_{12} during pernicious anemia treatment: a case report

Jessica Morales-Gutierrez, Sebastián Díaz-Cortés, María A. Montoya-Giraldo and Andres F. Zuluaga

CIEMTO [Drug and Poison Research and Information Center], Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia

ABSTRACT

Context: The clinical consequences of excess vitamin B_{12} induced by multiple oral doses of cyanocobalamin are not well-known.

Case details: A young woman was treated with multiple daily doses of 1 mg of cyanocobalamin for severe pernicious anemia. After a total dose of 12 mg, she developed acne, palpitations, anxiety, akathisia, facial ruddiness, headache, and insomnia. She improved two weeks after stopping the drug. There were no sequelae nor complications.

Discussion: Although these symptoms of cobalamin toxicity were unexpected and unusual, the case reminds us that the administration of any drug is not entirely safe.

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Introduction

Vitamin B_{12} or cobalamin is a water-soluble micronutrient essential for human metabolism acting as an enzymatic cofactor in the formation of red blood cells, DNA repair, RNA transcription, among other functions [1]. The prevalence of cobalamin deficiency ranges between 5 and 40%, and may result from pernicious anemia, intestinal malabsorption or a strict vegan diet [2].

Cyanocobalamin and hydroxocobalamin are the primary forms of vitamin B_{12} in clinical use [1]. A single megadose of 5 g of hydroxocobalamin is recommended as cyanide antidote, and the most common adverse reactions included transient chromaturia, erythema, acneiform rash, increased blood pressure, nausea, and headache. However, reports describing the toxic effects induced by multiple doses of cobalamin products during non-antidotal therapeutic uses are infrequent [1].

Here we report the onset of acne, among other clinical manifestations in a young patient, secondary to the parenteral administration of repeated doses of cyanocobalamin.

Case description

During a routine medical review, a 24-year-old hispanic woman with a history of psoriasis, manifested mild thyroid goiter that was related to Hashimoto's thyroiditis (anti-TPO antibodies of 819 IU/mL and anti-TG of 193 IU/mL), plus a cobalamin deficiency with a serum B_{12} level of 50 pg/mL (normal range: 187–883 pg/mL). At that moment, the patient did not report the consumption of any medication, nor any herbal product.

Renal function was adequate. The serum levels of apolipoprotein B, lipoprotein A, vitamin D, folic acid, TSH, free T4, total T3, PTH, FSH, LH, cortisol, somatomedin C, estradiol and blood ferritin were standard. High serum levels were documented for total cholesterol (267 mg/dL), LDLc (159 mg/dL), prolactin (32.8 ng/mL), somatotropin (10.4 ng/mL), gastrin (947 pg/mL), and antibodies against parietal cells (1:640 dilution).

Based on these results, the endocrinologist prescribed 1 mg per day of intramuscular cyanocobalamin for six days, continuing with 1 mg weekly until completing a month. After three weeks, the patient stopped the treatment due to general discomfort. As a serum B12 level of 366 pg/mL (low-normal level) was obtained, the endocrinologist ordered to re-start the treatment of 1 mg daily for another six days. Three days later, the patient noticed for the first time the appearance of acneiform eruptions on the forehead, chin, neck, chest, and back. On the fourth day, she manifested palpitations, anxiety, akathisia, facial ruddiness, headache, and insomnia. Therefore, she decided to stop the treatment again. After 72 h the symptoms still persisted, especially anxiety and insomnia, requiring mexazolam 1 mg p.o. daily for two doses, with partial improvement. Almost all symptoms disappeared in the following week, but the acneiform eruption improved only after two weeks. Then, a serum B_{12} level of 1858 pg/mL was finally reported.

For this report, the patient informed consent was obtained and the CARE guidelines were adopted.

Discussion

Here we reported the toxicity induced by high doses of cyanocobalamin in a young woman with multiple

CONTACT Andres F. Zuluaga andres.zuluaga@udea.edu.co Carrera 51D # 62-42, Oficina 210, Medellín, Antioquia, Colombia

autoimmune disorders as thyroiditis and pernicious anemia. The association between pernicious anemia and other autoimmune diseases such as type 1 diabetes, autoimmune thyroiditis, or vitiligo is well-known [3].

Cobalamin absorbed from animal food in the diet is stored by the liver as coenzyme B_{12} [1]. The deficiency of vitamin B_{12} causes a reduction in the synthesis of S-adenosyl methionine and consequently, DNA methylation [4]. Likewise, the inhibition of methylenetetrahydrofolate reductase decreases, resulting in the irreversible conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which eventually leads to nucleic acid damage by aberrant uracil incorporation to DNA [4]. Additionally, in the metabolism of homocysteine (Hcy), coenzyme B12 is converted into methionine by the action of methionine synthase [4], therefore, in deficiency, the synthesis process is disturbed inducing hyperhomocysteinemia [4]. The altered DNA methylation and the increase in Hcy are both risk factors for cancer and cardiovascular disease, respectively [1,4,5].

The manufacturer recommended dose in pernicious anemia is 0.1 mg IM/SC once daily for 6–7 days, then every other day for seven doses, then every 3–4 days for 2–3 weeks, then monthly [6]. There is an alternative parenteral high-dose of 1 mg IM/SC once daily for six days, continuing with 1 mg weekly for one month, up to a cumulative dose of 10 mg [2]. Glass et al. demonstrated that this dosage schedule in older patients with a deficit of cyanocobalamin (185 ± 44 pg/mL) results in an average of 2634 ± 1470 pg/mL without additional doses required [7]. Unexpectedly, this dosing schedule was unsuccessful for our patient. Some authors consider that "because there are no reports of adverse effects associated with excess vitamin B_{12} intake", there is no reason to advise against dose duplication [1]. According to our case, we beg to disagree.

Cyanocobalamin has been considered a very safe medicine, with few reports in the medical literature of adverse effects (ADE) associated with its use, even using single megadoses as an antidote in cyanide poisoning. During the last 50 years, VigiAccess™ has 1692 records of ADE associated with cyanocobalamin [8], 63% of them recorded between 2010 and 2018. Skin and subcutaneous disorders, general disorders and administration site conditions (i.e. injection site pain, fatigue, pyrexia, pain), nervous system disorders (i.e. anxiety and insomnia) and gastrointestinal disorders (i.e. nausea, diarrhea, vomiting) represent 57% of all ADE. Pruritus, rash, and urticarias were the main skin disorders described (424 cases), but acne or acneiform eruptions only accounted for 51 reports.

The clinical consequences of hypercobalaminemia are not well-known. In some reports, acneiform eruptions appear to be one of them, as in our case (Figure 1) [9–11]. The proposed pathogenesis is that cobalamin modulates the transcriptional and metabolic activities of *Propionibacterium acnes* in the human skin [12]. Paradoxically, supraphysiological vitamin B_{12} levels $>$ 950 pg/mL can result in clinical signs of cobalamin deficiency [5]. A simulated PK profile using our patient cyanocobalamin dosing schedule showed that repeated doses easily achieve supraphysiological levels, despite the initial low B_{12} serum concentrations reported (Figure 2).

Conclusion

The skin and CNS toxicity observed here may have been the result of repeated, high doses of cyanocobalamin. It should

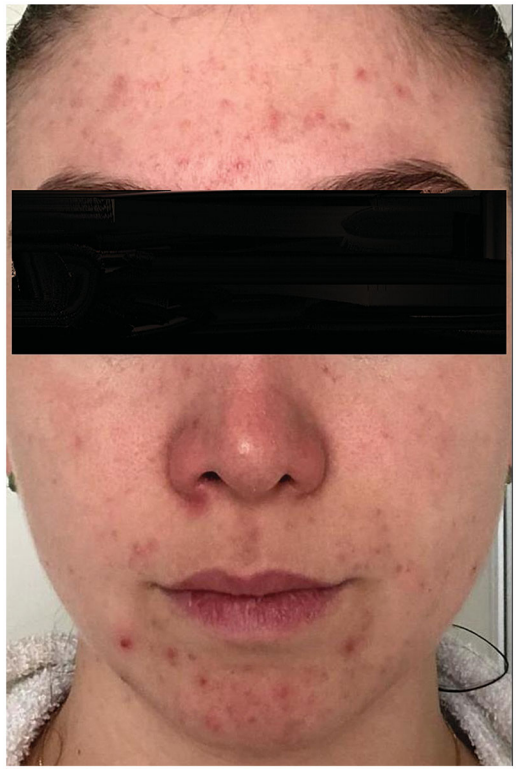

Figure 1. Acneiform eruption that onset after repeated, high doses of cyanocobalamin in the patient.

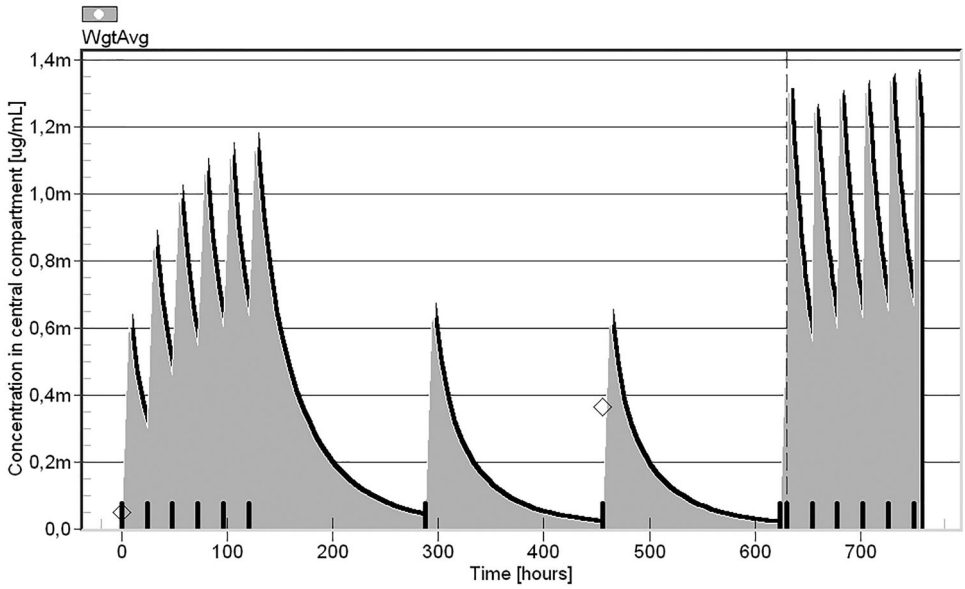

Figure 2. A non-parametric population pharmacokinetic model of cyanocobalamin was built in Pmetrics (data not shown) [13] using the raw data published by Tillemans et al. [11]. A single compartment model fitted to data. The mean parameter estimates absorption rate constant ($2.29 \pm 1.08\ h^{-1}$), elimination rate constant ($0.04 \pm 0.03\ h^{-1}$), bioavailability (0.70 ± 0.06) and volume of distribution (15.7 ± 6.17 L) were obtained and used to explore the dosage regimen used in our clinical case with a multiple model Bayesian adaptive control [14]. Each dose administered is marked in the *x*-axis. The solid black lines and gray shaded areas represent the weighted average concentration-time profile of cobalamin simulated for our patient. The diamonds represent the vitamin B_{12} levels obtained as a baseline (50 pg/mL) and as a control (366 pg/mL). Values higher than 950 pg/mL, were considered supraphysiologic. Values in *y*-axis should be divided by 1000 to obtain the raw data in pg/mL.

remind healthcare providers to be cautious with this vitamin, because no drug is entirely safe.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

María A. Montoya-Giraldo http://orcid.org/0000-0002-3756-0074
Andres F. Zuluaga http://orcid.org/0000-0001-5656-4153

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