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LETTER TO THE EDITOR

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Vitamin B12 allergy and desensitization

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I read the article titled “Fewer injections, less pain: Successful cyanocobalamin desensitization,” by Yegin Katran and Bulut with great interest.¹ In this article, the authors described the development of painless oral desensitization to a drug with painful injections, which is different from the subcutaneous route mentioned in the literature. Nevertheless, clarifying some issues that are not fully understood about the case and methodology would improve readers’ understanding of the article and the concerned literature.

Although allergic/hypersensitivity reactions to cyanocobalamin or hydroxycobalamin are rare, a few case reports are reported.²⁻⁶ The mechanism of hypersensitivity to vitamin B12 is not understood completely; both immunological and non-immunological mechanisms may contribute to hypersensitivity. Immunological drug hypersensitivity is mainly mediated by immunoglobulin E (IgE; immediate-type, type 1 hypersensitivity reactions) and by delayed cellular (type IV) reactions. Non-immunological drug hypersensitivity is primarily thought to be pharmacological interactions and pseudoallergies.⁷ It would have been better to mention these mechanisms in the article.¹

The desensitization protocol is performed in these cases if no suitable alternative drugs are available for drug allergy. Unfortunately, there is no standardized protocol for vitamin B12 desensitization, similar to those available for antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). The desensitization protocol developed by Caballero et al.⁴ was successfully applied to most hydroxycobalamin⁶ and cyanocobalamin allergic patients as reported in the literature. In this protocol, intramuscular administration of parenteral products for desensitization is painful; hence, subcutaneous desensitization is often applied. Different desensitization protocols are described.²⁻⁷ The entire desensitization cycle lasts for 1-5 days and includes 10-11 intramuscular/subcutaneous injections. In 1-day protocols, the desensitization cycle ranges from a 1½-h rush protocol to a 7-h standard protocol.⁷ Any drug desensitization is time-dependent, and re-sensitization recurs eventually.⁴ It is shown by intradermal tests to persist for at least 4 weeks to 6 months.⁷

The unique aspects of this case study included the use of oral desensitization instead of subcutaneous desensitization, which differed from the literature and was first reported by Alves-Correia et al.² Cyanocobalamin was started at a higher dose of 20 mcg, and monthly applications followed a 1-day protocol. The interim reminder doses as described in the

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protocols of Kartal et al.³ and Caballero et al.⁴ were not administered on days 7 and 21, and the desensitization protocol was continued with monthly repetitions instead of these reminder doses. The issue here is how oral desensitization can be effective in a 56-year-old patient with pernicious anemia because of gastric/intestinal malabsorption.⁷ In case of intestinal malabsorption, parenteral routes (subcutaneous and intramuscular) are usually preferred due to the difficulty of absorption. However, interestingly, there was no problem with the intramuscular preparation given after desensitization.¹

Some limitations of the case report include the following: There are reports in the literature of patients who reacted to one form of cobalamin but tolerated an alternative formulation. However, sensitization to all injectable formulations of vitamin B12 and *in vitro* cross-reactivity between all cobalamins have been demonstrated. In this study, the authors did not have hydroxycobalamin on hand, so it is not known whether there was cross-reactivity in this patient or whether hydroxycobalamin could be used instead of cyanocobalamin.⁶ Further advanced laboratory tests, such as basophil activation or histamine release test, specific IgE test, etc., could not be performed for the IgE-mediated type 1 reaction. Skin prick test (SPT) with cyanocobalamin was performed in this study. However, negative and positive control test results were not reported in this SPT.¹ Supposedly, an intradermal test was not performed because the SPT was positive, and drug provocation was not performed because anaphylaxis developed in the patient.¹ The preparation of cyanocobalamin used in Türkiye contains benzyl alcohol as a preservative,⁵ which was involved in a patient reacting to vitamin B12 injection, as reported in the literature.⁴ I wonder whether the authors considered this when they did some of the tests and evaluations.

Minor points: Punctuations of some words (e.g., intramuscular, solution, application) were incorrect in the article.¹ Spellings of some words and definitions in the text were also incorrect. For example, “mL” instead of “cc,” and “because of” was more correct than “becaue of.”

In conclusion, I would like to thank the authors for this high-quality case report and the results for evoking awareness about the diagnosis and management of vitamin B12 allergy and hypersensitivity reactions.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Conflicts of Interest

None.

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