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LETTER TO THE EDITOR

What biological markers could be used for diagnosis and monitoring of nitrous oxide abuse?

We carefully read the article published in the *European Journal of Neurology* entitled "How to distinguish Guillain-Barré syndrome from nitrous oxide-induced neuropathy: a 2-year, multicenter, retrospective study" [1]. We aim to propose suggestions regarding the use of vitamin B12 as a biomarker of nitrous oxide (N_2O) intoxication.

CLINICAL PRESENTATION VARIES IN N_2O INTOXICATION

Fortanier et al. established criteria to define the Guillain-Barré syndrome (GBS)-like group; however, clinical symptoms of N_2O exposure vary. Clinical and cerebrospinal fluid analysis can be available rapidly and guide treatment decisions. In case of uncertainty between GBS and N_2O-induced neuropathy, intravenous immunoglobulins must be initiated for critical patients, without waiting for biological laboratory test results.

PATHOPHYSIOLOGY OF N_2O EXPOSURE DEMONSTRATES THAT VITAMIN B12 IS NOT AN APPROPRIATE BIOMARKER

Clinical symptoms of N_2O exposure are related to the functional inactivation of vitamin B12 by oxidation of its cobalt ion [2]. This oxidation prevents the formation of methylcobalamin, resulting in a decrease in methionine synthase activity which converts homocysteine into methionine. A similar action is suspected for MMA-CoA mutase, which converts methylmalonic acid (MMA) into succinyl-CoA (Figure 1).

Fortanier et al. only focused on the significance of serum vitamin B12 measurement, a routine laboratory test providing results within a few hours. However, as N_2O leads to functional inactivation of vitamin B12, quantitative deficiency is secondary and inconsistent [3]. In N_2O abuse, vitamin B12 is neither specific (prevalence of about 25% in the general population) nor sensitive: only about 50% of N_2O consumers exhibit vitamin B12 deficiency [1, 3].

Functional exploration of vitamin B12 with plasma homocysteine and MMA gives informative results. These measurements were conducted but not discussed by the authors. However, as vitamin B12, homocysteine can be measured rapidly [4].

PLASMA HOMOCYSTEINE IS A MARKER OF RECENT N_2O CONSUMPTION

Homocysteine increases rapidly, and it is a sensitive biomarker for recent N_2O consumption [3]. As reported by Fortanier et al., the majority of patients (96.2%) have elevated plasma homocysteine levels [1]. However, homocysteine lacks specificity: it also rises in cases of

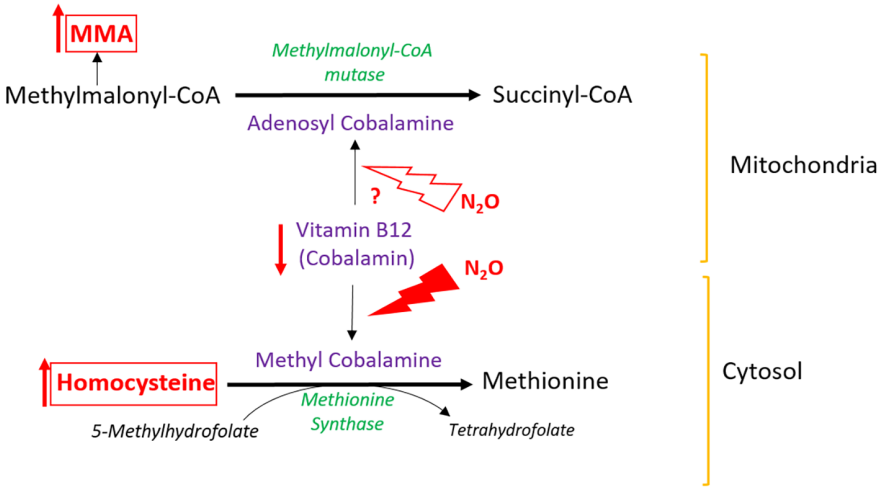

FIGURE 1 Metabolic impact of nitrous oxide (N_2O) on cobalamin pathways.

vitamin B9 or B12 deficiency, renal or hepatic insufficiency, hypothyroidism, and in certain metabolic disorders.

PLASMA MMA IS A MARKER OF CLINICAL SEVERITY OF N_2O ABUSE

Plasma MMA is a reliable marker of functional vitamin B12 deficiency. Plasma MMA lacks sensitivity in N_2O intoxication as its elevation is not consistent, but is correlated with the clinical severity [3]. Plasma MMA is more specific than homocysteine in the assessment of vitamin B12 deficiency as it is independent of vitamin B6 and B9 status, but rises in cases of renal insufficiency and in certain metabolic diseases.

IN THE CONTEXT OF N_2O CONSUMPTION A COMBINATION OF BIOMARKERS IS RECOMMENDED

In the context of N_2O abuse, high plasma homocysteine suggests recent consumption, and plasma MMA can aid evaluation of the clinical severity [5]. Vitamin assays (B6, B9, B12) may uncover nutritional deficiencies. Consequently, it is important to exclude other causes of homocysteine or MMA elevation.

The European Federation of Laboratory Medicine is in the process of formulating guidelines concerning the use of biological parameters for initial evaluation and follow-up of N_2O intoxication (https://www.eflm.eu/site/page/a/1832).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Fortanier E, Berling E, Zanin A, et al. How to distinguish Guillain-Barré syndrome from nitrous oxide-induced neuropathy: a 2-year, multicentric, retrospective study. *Eur J Neurol*. 2023;30:3296-3306.
2. Mair D, Paris A, Zaloum SA, et al. Nitrous oxide-induced myeloneuropathy: a case series. *J Neurol Neurosurg Psychiatry*. 2023;94:681-688.
3. Grzych G, Deheul S, Gernez E, et al. Comparison of biomarker for diagnosis of nitrous oxide abuse: challenge of cobalamin metabolic parameters, a retrospective study. *J Neurol*. 2023;270(4):2237-2245.
4. Badiou S, Bariolet S, Dupuy AM, Sultan A, Avignon A, Cristol JP. A new DiaSys colorimetric assay for plasma homocysteine: application in diabetic patients. *Ann Clin Lab Sci*. 2009;39(3):233-240.
5. Gernez E, Bennis A, Diesnis R, Niguet JP, Grzych G. Awareness of health care related to nitrous oxide abuse for diagnosis, treatment and follow-up. *Ir J Med Sci*. 2023;192:3087-3089.