

Case report

Hypercobalaminemia Induced by an Energy Drink after Total Gastrectomy: A Case Report

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Abstract

We encountered a case of hypercobalaminemia induced by oral intake of an energy drink after total gastrectomy. The patient was referred to our hospital due to findings suspicious for gastric cancer on screening. A 20 mm type 0-IIc lesion was detected in the gastric subcardia on esophagogastroduodenoscopy. Total gastrectomy followed by Roux-en-Y reconstruction was performed. He was discharged without complications. His basal serum vitamin B₁₂ level was initially maintained with monthly intramuscular injections of vitamin B₁₂. After 9 months, his serum vitamin B₁₂ level suddenly increased up to 36-fold higher than the normal range and persisted there for one year without vitamin B₁₂ injections. The patient ultimately reported consuming half a bottle of an energy drink each day during this time period. This case demonstrates the risk of unexpected hypervitaminemia resulting from self-administration of nutritional supplements.

Key words: hypercobalaminemia, total gastrectomy, energy drink, supplement, transcobalamin

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Introduction

In recent years, supplements and energy drinks have become very popular due to their low cost and wide availability. However, several reports have emerged warning of side effects and even death caused by excessive intake^{1–3}.

Here we report a patient with hypercobalaminemia induced by regular intake of an energy drink after total gastrectomy. Vitamin B₁₂ is a water soluble vitamin absorbed in conjunction with intrinsic factor (IF) that is produced by the gastric mucosa⁴. Excess vitamin B₁₂ is excreted by the kidneys, which accounts for the lack of persistent hyperco-

balaminemia under normal conditions⁴. However, recently, there have been several reports of elevated serum vitamin B₁₂ levels associated with multivitamin use in patients after total gastrectomy^{5, 6} and patients with pernicious anemia⁷. This case was interesting because extreme hypercobalaminemia was induced by oral intake after total gastrectomy and persisted in a healthy individual after gastrectomy.

Case Report

The patient was a 76-year-old man referred to our clinic with screening results suspicious for gastric cancer. His past medical history consisted of hypertension and benign prostatic hypertrophy. Physical examination and laboratory data were nonspecific except for asymptomatic macroamylasemia. Esophagogastroduodenoscopy showed a 20 mm type 0-IIc lesion in the gastric subcardia, preoperatively diagnosed as cT1, cN0, cM0, cP0, cStage IA. The patient underwent a planned total gastrectomy with D1 lymphadenectomy followed by Roux-en-Y reconstruction with no complications. The postoperative course was unremarkable, and the patient was discharged on postoperative day 10. Pathologic evaluation revealed an 8 mm moderately differentiated tubular adenocarcinoma on the anterior wall. Macroscopically, the tumor was flat and slightly depressed (type 0-IIc). Histologically, it showed an INFβ growth pattern, and the tumor invaded the submucosa (pT1 SM). There was no evidence of lymph node (pN0) or liver (pH0) metastasis or venous (v0) or lymphatic (ly0) invasion. The proximal and distal resection margins were clear. Peritoneal cytology was also negative (pP0, CY0). The final stage was pT1N0M0, Stage IA according to the Japanese classification of gastric carcinoma staging system⁸.

Except for occasional heartburn, a sense of abdominal distension, and elevated serum amylase levels, he had no ob-

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Table 1 Laboratory data after total gastrectomy

<Complete blood count>		<Biochemistry>		<Viral markers>	
WBC	8,100/ μ l	Sodium	140 mEq/l	HBsAg	(-)
Neutrophils	47.50%	Potassium	3.8 mEq/l	HCVAb	(-)
Lymphocytes	44.50%	Chloride	104 mEq/l	HIV	(-)
Monocytes	5.00%	Calcium	9.4 mg/dl		
Eosinophils	3.00%	BUN	15.9 mg/dl	24 hr Ccr	72 ml/min
Basophils	0.00%	Cre	0.78 mg/dl		
Hb	13.2 g/dl	TP	6.2 g/dl		
PLT	24×10^4 / μ l	Alb	3.1 g/dl		
		AST	20 U/l		
		ALT	17 U/l		
		LDH	203 U/l		
		ChE	219 U/l		
		T-Bil	0.6 mg/dl		
		ALP	317 U/l		
		γ -GTP	18 U/l		
		AMY	1205 U/l		

BT, bleeding time; Ccr, creatinine clearance.

vious signs and symptoms during postoperative follow-up. He took nifedipine (Adalat CR[®], Bayer Healthcare, Osaka, Japan), theophylline (Theodur[®], Mitsubishi Tanabe Pharma, Tokyo, Japan), etizolam (Depas[®], Mitsubishi Tanabe Pharma), bifidobacterium (Lac-B Granular Powder[®], Kowa Company Ltd., Nagoya, Japan), magnesium hydrate (Yoshida Pharmaceutical, Tokyo, Japan) and eviprostal (Eviprostal[®], Nippon Shinyaku, Kyoto, Japan). His basal serum vitamin B₁₂ level was followed monthly and initially maintained within the normal range by intramuscular injections of mecobalamin (Methycobal[®], Eisai, Tokyo, Japan). Nine months after surgery, his serum vitamin B₁₂ levels suddenly increased to 33,000 pg/ml, which is approximately 36-fold higher than the normal range (233–914 pg/ml). This level of hypercobalaminemia persisted for approximately one year without mecobalamin injections. The patient's diet did not contain any obvious excess sources of vitamin B₁₂. Fortunately, he did not show any obvious symptoms or laboratory abnormalities (Table 1). He later reported that he had started drinking half a bottle of an energy drink as a supplement during this time. After he discontinued the energy drink, his serum vitamin B₁₂ levels quickly declined to within the normal range (Figure 1). The ingredients on the energy drink label included caffeine, fructose, β -carotene, vitamins B₂, B₆ and C, octacosanol, garlic, licorice, ginseng, bracket fungus, *Polygonatum falcatum* and chlorella extract; there was no mention of vitamin B₁₂. Concentration analysis revealed an undetectable amount of vitamin B₁₂ in the energy drink.

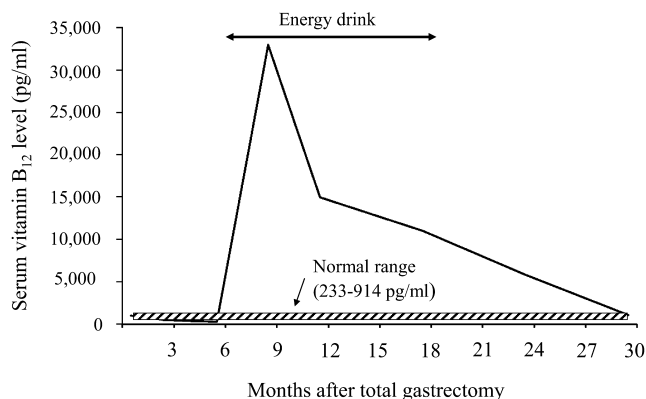


Figure 1 Serum vitamin B₁₂ levels after total gastrectomy. After total gastrectomy, the basal serum vitamin B₁₂ level was initially maintained within the normal range by intramuscular injections of mecobalamin (Methycobal[®]). Nine months after surgery, the serum vitamin B₁₂ level suddenly increased to 33,000 pg/ml and remained persistently elevated for approximately one year without injections of mecobalamin. During that time, the patient consumed half a bottle of an energy drink each day as a supplement. After discontinuing the drink, the serum vitamin B₁₂ concentration declined to within the normal range.

Discussion

Vitamin B₁₂ is one of the vitamins not produced by the human body; therefore, it is essential to ingest it through food such as meat, fish and shellfish. Recently, it was clarified that there are two pathways for vitamin B₁₂ absorption,

i.e., a conventional IF-dependent pathway and an IF-independent pathway⁹). In the IF-dependent pathway, hydrochloric acid produced by the gastric mucosa cleaves vitamin B₁₂, which is bound to protein in food. The released vitamin B₁₂ attaches to R-protein and passes into the duodenum, where R-protein is removed and free vitamin B₁₂ binds to IF⁴). The IF-vitamin B₁₂ complex binds to a receptor located on the luminal membrane of the distal ileum. The IF-independent pathway involves passive diffusion in the ileum that is dependent on the vitamin B₁₂ concentration⁴). In healthy individuals, the IF-independent pathway accounts for only 2–5% of vitamin B₁₂ absorption¹⁰). Therefore, the IF-independent pathway is usually not sufficient to meet daily requirements. However, previous reports indicate that high oral intake can result in sufficient serum levels of vitamin B₁₂ in patients who have a defect in the normal absorption pathway^{5–7, 11}). Kim *et al.*⁶) reported that patients who received total gastrectomy were successfully maintained within the normal range by oral intake of 1500 µg of vitamin B₁₂ daily. In our preliminary study, 15 patients who took 750 µg/day of oral multivitamins (Vitamedin[®], Daiichi-Sankyo, Tokyo, Japan) for 6 months after total gastrectomy showed increases in serum vitamin B₁₂ levels from 192 ± 26 pg/ml to 571 ± 215 pg/ml (p<0.001, unpublished data). However, the elevation in the serum vitamin B₁₂ level by the IF independent pathway is usually at most to the upper limit of the normal range. In the present patient, before analysis of the energy drink, we attributed his extreme hypercobalaminemia to the high concentration of vitamin B₁₂ in the energy drink absorbed through the IF-independent pathway. However, since the concentration of vitamin B₁₂ was undetectable in the energy drink, it was unlikely that passive absorption accounted for this hypercobalaminemia.

In the serum, vitamin B₁₂ is bound to proteins known as transcobalamins (TCs)⁴). Approximately 80% of serum vitamin B₁₂ is transported on inactive TC I. The active transport protein for vitamin B₁₂ is TC II, which carries the remaining 20% in the circulation⁴). Vitamin B₁₂ in the circulation that exceeds the binding capacity of TCs is rapidly excreted in the urine, which explains why persistent hypercobalaminemia does not occur under normal conditions⁴). Persistent hypercobalaminemia can occur under pathological conditions such as renal failure, liver disease¹²), myeloproliferative disease¹³), infections¹⁴), and emergence of autoantibodies to TCs¹⁵). It has been hypothesized that inflammation-induced hepatocyte degradation in liver disease causes the release of vitamin B₁₂ into the circulation¹²). Zittoun *et al.*¹³) reported that myeloblasts contain increased levels of TC II, which induces high serum TC II concentrations in patients with myeloproliferative disease. Cheeramakara *et al.*¹⁴) stated that the mononuclear phagocytic system stimulated by scrub ty-

phus infection increased synthesis and release of TC II into the circulation, leading to a serum vitamin B₁₂ concentration as high as 3,000 pg/ml. Carmel *et al.*¹⁵) described that circulating autoantibody to TC II resulted in retention of both TC II and vitamin B₁₂ due to impaired clearance and that the serum vitamin B₁₂ concentration increased up to 22,000 pg/ml. The authors further described that the autoantibody was induced by infections and that the serum vitamin B₁₂ level fell with clinical improvement.

In this case, the patient did not have renal failure, liver disease or myeloproliferative disease. Although we were unable to examine the amount of TCs in this patient, there were two possibilities that could explain the hypercobalaminemia, i.e., stimulation of mononuclear phagocytic systems or production of antibody to TC II. Ginseng and garlic, constituents of this energy drink, were reported to activate macrophage functions through activation of transcription factors such as NF-κB, AP-1, ERK and JNK^{16, 17}). It was possible that macrophages and monocytes were activated by some constituents in the energy drink, which increased synthesis and release of TC II into the circulation and induced hypercobalaminemia. On the other hand, despite no direct evidence that herbal extracts induce production of anti-TC II antibodies, some herbal extracts actually induce production of autoantibodies^{18, 19}). Wada *et al.*¹⁸) described that ginseng induced production of myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA), which subsequently resulted in rapidly progressive MPO-ANCA-associated vasculitis. Yuce *et al.*¹⁹) reported that noni juice from morinda citrifolia stimulated generation of liver-kidney microsomal type 1 antibody, leading to subacute liver failure. In the present case, since the serum concentration of vitamin B₁₂ increased up to 33,000 pg/ml, we speculate that anti-TC II antibody might have been produced by some constituents in the energy drink rather than by stimulation of mononuclear phagocytic systems.

The market value of nutritional supplements and energy drinks is continually growing, and annual consumption is increasing²⁰). The known and unknown pharmacology of these products raises concern for potentially serious adverse effects. Barton *et al.*¹) reported iron overload due to daily intake of iron supplements, manifested as hemochromatosis, arthritis, pigmentation and atherothrombosis. Mursu *et al.*²¹) reported that daily oral intake of multivitamins, folic acid, magnesium, zinc or copper was associated with increased risk of overall mortality in older women. Further, four documented cases of caffeine-associated death^{3, 22}), four separate cases of seizures²³) and one case of mania²⁴) were associated with the consumption of energy drinks. Worthley *et al.*²⁵) reported that energy drink consumption acutely increases platelet aggregation and blood pressure, impairing endothe-

lial function and increasing the risk of myocardial infarction in healthy young adults. Most energy drinks contain natural products such as guarana, ginseng and taurine; however, no reports of associated negative effects were found, since their concentrations in many energy drinks are usually below the level expected to deliver either therapeutic benefits or adverse events²⁶. The most commonly reported adverse effects seem to be related to caffeine²⁶. No known symptoms have been reported in hypercobalaminemia alone⁴, since hypercobalaminemia is usually accompanied by specific health conditions such as renal failure, liver disease and infections. No previous reports have described a healthy person with such a high serum vitamin B₁₂ level as in this case. Except for occasional heartburn and a sense of abdominal fullness, which seemed to be related more with postoperative symptoms, the patient complained of no other symptoms. However, there is no guarantee that he would not show serious symptoms if he kept on taking the energy drink.

Conclusion

We encountered a patient with hypercobalaminemia associated with daily intake of an energy drink after total gastrectomy. Nutritional supplements and energy drinks have exploded in popularity in the past several years; however, their use is not without risk. This case report demonstrates the risk of unexpected hypervitaminemia when patients self-administer such products.

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