BRIEF REPORT

Renal Failure in a Soldier Taking N.O.-Xplode

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Introduction: **Dietary supplements are widely used but are unregulated by the US Food and Drug Administration. Presented here is a case of severe renal failure possibly associated with a dietary supplement, which demonstrates the need for improved patient–physician communication regarding the possible risks and lack of regulation of dietary supplements.**

Methods: **A 26-year-old man presented with 3 days of flank pain. The patient had been taking a dietary supplement called N.O.-Xplode for 3 months. Initial laboratory tests revealed a creatinine value of 9.45 mg/dL. Extensive laboratory analysis and imaging revealed no underlying cause of his renal injury. Renal biopsy showed acute tubular necrosis with normal glomeruli. After discontinuing N.O.-Xplode, renal function returned to normal within 1 week.**

Conclusions: **This case demonstrates the need for improved patient–physician communication about dietary supplements. The patient had not consulted a physician before initiating use; the amount of each ingredient contained in the dietary supplement is unavailable; and there are no available data regarding safety or efficacy. It is critical that physicians are able and open to counseling patients on the inherent risks associated with dietary supplements, including their lack of regulation by the Food and Drug Administration, unknown efficacy, and possible serious adverse outcomes. (J Am Board Fam Med 2014;27: 565–569.)**

Keywords: **Case Reports, Dietary Supplements, Kidneys, Renal Failure**

Over half of American adults use dietary supplements, and yet patients often are not aware of how these substances are regulated or their potential risks.[1] The 1994 Dietary Supplement Health and Education Act defines dietary supplements as a product that is intended to supplement the diet and contains a single or combination of vitamins, minerals, herbs, botanicals, amino acids, dietary substances, concentrates, metabolites, constituents, and/or extracts.[2] The Dietary Supplement Health and Education Act significantly deregulated dietary supplements, classifying them as a food, such that there is now no Food and Drug Administration approval process to ensure efficacy and safety before commercial availability.[2] Dietary supplements have since become more widely accessible by the general public, and prevalence of their use is increasing.[1]

Despite their widespread use and potential to influence health outcomes, comprehensive guidance regarding dietary supplements is often not provided to patients. A 2013 meta-analysis examined the content of discussions regarding dietary supplements between patients and primary care providers; efficacy or safety was addressed only approximately 17% of the time.[3] This communication gap is likely a manifestation of a multifactorial problem rooted in lack of patient disclosure, deficits in physician knowledge, and poor public awareness of the regulatory process.[3–5]

Presented here is a case of severe renal failure in a previously healthy young man taking N.O.-Xplode, a dietary supplement manufactured by Bio-Engineered Supplements and Nutrition. This case describes a potential serious adverse outcome related to a dietary supplement that has not previously been reported. Moreover, it demonstrates the need for improved patient–physi-

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cian communication and increased public awareness of the risks and lack of regulation of dietary supplements.

Case Presentation

A 26-year-old white man presented to the emergency department with 3 days of flank and abdominal pain associated with nausea, decreased appetite, and pink-tinged urine. He denied fever, chills, dysuria, or change in bowel habits. At presentation his blood pressure was 154/81 mmHg. The remainder of his vital signs were within normal limits. No costovertebral angle tenderness or edema were present, and he appeared well hydrated with moist mucus membranes, normal skin turgor, and brisk capillary refill. Mild diffuse abdominal tenderness was the only significant examination finding.

The patient was previously healthy, had never been hospitalized or had surgery, and was taking no medications. He was an active duty Army soldier who, for the past 3 months, was performing a vigorous weight training program and taking N.O.-Xplode. The patient was taking the supplement according to instructions on the label, which direct consumers to mix 1 scoop (about 20 g) of N.O.-Xplode powder with 5 to 6 oz of water 3 times daily on training days and once daily on nontraining days. He denied use of any other supplements or over-the-counter medications, including anabolic steroids and nonsteroidal anti-inflammatory medications.

Initial laboratory tests revealed a creatinine concentration of 9.45 mg/dL, consistent with an estimated glomerular filtration rate (eGFR) of 6.8. Urinalysis showed +1 red blood cells and +1 protein with no urine eosinophils. Microscopic urine sediment analysis was bland, showing no dysmorphic cells or casts. He was subsequently hospitalized for further workup. Creatinine peaked at 10.64 mg/dL on hospital day 1. Urine output remained normal throughout admission. No electrolyte derangements were initially present, but hyperkalemia developed and peaked on hospital day 2, with a potassium concentration of 6.2 mEq/L. Blood pressure peaked at 182/94 mmHg on hospital day 3. Renal ultrasound and computed tomography were unremarkable.

The severity of renal failure in this patient was concerning, indicating rapidly progressing glomerular nephritis, and a renal biopsy was obtained. However, without a definitive diagnosis and while awaiting return of the biopsy results and pending serology test results, he was empirically treated with 3 days of high-dose intravenous steroids starting on hospital day 4.

Antistreptolysin-O titer was slightly elevated at 406 IU/mL, but complement levels were not depressed, so postinfectious glomerulonephritis was ruled out. Creatine kinase was not elevated, so rhabdomyolysis was ruled out. Antiglomerular basement membrane antibody, serum protein electrophoresis, treponema palladium antibody, antinuclear antibodies, human immunodeficiency virus, anti-DNA antibody, DNase B antibody, proteinase 3 antibody, and hepatitis C virus antibody tests all returned normal.

Renal biopsy showed acute tubular necrosis with normal glomeruli. Immunofluorescence studies did not demonstrate immune complex–type deposits. Electron microscopy did not show electron-dense deposits or abnormalities in the glomerular basement membranes.

Six days after presentation, creatinine had improved to 2.1 mg/dL (eGFR, 38.4). He was discharged with an oral steroid taper and emphatically instructed to discontinue taking N.O-Xplode. Nine days after initial presentation, at an outpatient follow-up appointment, creatinine had returned to normal (1.07 mg/dL; eGFR, 83.5), blood pressure and electrolytes remained normal, and symptoms of abdominal pain and nausea had resolved. Before his hospitalization, the patient had not discussed N.O.-Xplode with his primary care provider.

Discussion

With no evidence of alternative etiologies, the severe renal failure in our patient may be associated with his use of N.O.-Xplode. This dietary supplement is marketed to young adults to increase muscle mass and contains a proprietary blend of creatine, nitric oxide, caffeine, medium chain triglycerides, amino acids, vitamin B_6, vitamin B_{12}, folate, and an electrolyte replacement solution (Figure 1). Since 2009 there have been several reported cases of adverse outcomes linked to N.O.-Xplode, including a case series of 12 patients with mild to moderate hepatitis,[6] one case of ischemic colitis,[7] and one case of palpitations and headache.[8] The patient presented here is the first documented case of renal failure in someone taking N.O.-Xplode. Even after a pattern of adverse outcomes, N.O.-Xplode remains available to the public and carries no safety warnings.

Figure 1. Contents label of N.O.-Xplode, a dietary supplement manufactured by Bio-Engineered Supplements and Nutrition. The amount of each ingredient within the N.O.-Xplode Proprietary Blend are not provided. The patient described in this case was previously healthy but developed severe renal failure while taking N.O.-Xplode.

SUPPLEMENT FACTS

Serving Size: 1 Scoop (20.5 g)
Servings Per Container: 50

	Amount Per Serving	% Daily Value
Calories	25	
Total Carbohydrates	6 g	2 %
Sugars	0 g	
Vitamin B6 (Pyridoxine HCL)	25 mg	1250 %
Folate (Vitamin B9)	400 mcg	100 %
Cyanocobalamin (Vitamin B12)	120 mcg	2000 %
Calcium	75 mg	8 %
Phosphorus	535 mg	50 %
Magnesium	360 mg	90 %
Sodium	230 mg	10 %
Potassium	75 mg	2 %
N.O.-XPLODE PROPRIETARY BLEND	18,000 mg	**
(Contains a Patented Nutrient Suspension Matrix & Efforsorb Delivery System)		
N.O. Meta Fusion		**
L-Arginine AKG, L-Citrulline Malate, RC-NOS (95% Rutacarpine), L-Citrulline AKG, L-Histidine AKG, NAD (Nicotinamide Adenine Dinucleotide), Gynostemma Pentaphyllum (95% Gyenosides) (leaves and stem)		
AVPT (Advanced Volumizing & Performance Technology)		**
Modified Glucose Polymers (Maltodextrin), Di-Creatine Malate, Trimethylglycine, Creatine Ethyl Ester-Beta-Alanine Dual Action Composite, Sodium Bicarbonate, Sodium Creatine Phosphate Matrix, Creatinol-O-Phosphate-Malic Acid Interfusion, Glycocyamine, Guanidino Propionic Acid, Cinnulin PF (Aqueous Cinnamon Extract) (Bark), Ketoisocaproate Potassium, Creatine AAB (Creatine Alpha-Amino-N-Butyrate)		
Ener-Tropic Xplosion		**
L-Tyrosine, Taurine, Glucuronolactone, Methylxanthine (Caffeine), L-Tyrosine AKG, MCTs (Medium Chain Triglycerides) (coconut), Lesser Periwinkle 99% Vinpocetine, 99% Vincamine, 99% Vinburine (whole plant)		
Phospho-Electrolyte Replacements		**
Di-Calcium Phosphate, Di-Potassium Phosphate, Di-Sodium Phosphate		
Gycerol Hydrating Polymers		**
Potassium Glycerophosphate, Magnesium Glycerophosphate, Glycerol Stearate		

Percent Daily Values are based on a 2.000 calorie diet. **Daily Value Not Established.

Other Ingredients: Citric Acid, Natural and Artificial Flavors, Potassium Citrate, Sucralose, Calcium Silicate, Acesulfame-K, FD&C Red #40, and FD&C Blue #1.

Due to settling, a natural occurrence with powders, variations in the powder height level may vary from bottle to bottle. Additionally, powder density may be affected as a result of the settling which may cause slight variation in the scoop serving size.

Allergen Warning: Manufactured on equipment which processes products containing milk, eggs, soybeans, shellfish, wheat, and tree nuts.

WARNING: Before consuming N.O.-XPLODE seek advice from a physician if you are unaware of your current health condition or have any pre-existing medical condition including but not limited to: high or low blood pressure, cardiac arrhythmia, stroke; heart, liver, or thyroid disease; anxiety, depression, seizure disorder, psychiatric disease, diabetes, pernicious anemia, difficulty urinating due to prostate enlargement, or if you are taking an MAO inhibitor or any other medications. Do not use if you are pregnant, nursing, prone to dehydration, or exposed to excessive heat. Reduce or discontinue use if sleeplessness, tremors, dizziness, nervousness, headaches, or heart palpitations occur. Please be aware that this product contains the naturally occurring amino acid Beta-Alanine, which may cause a tingling skin sensation, in some individuals similar to niacin flush. This effect should diminish after a few hours and should ultimately subside after days of continuous use. Although rare, individuals with the genetic disorder hyper Beta-Alaninemia should not use this product. N.O.-XPLODE is only intended to be consumed by healthy adults 18-50 years of age. Keep out of reach of children and pets.

These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent disease.

Table 1. Comparison of Patient Characteristics and Disease Courses Among Cases Describing an Association Between Creatine Supplementation and Renal Failure

Patient Characteristics	Case 1*	Case 2†	Case 3‡
Age (years)	20	24	26
Sex	Male	Male	Male
Creatine dosage	20 g daily for 4 weeks	5 g 3 times per week for 6 months	Unknown daily dose for 3 months
Presenting symptoms	Nausea, vomiting, flank pain, abdominal tenderness	Left flank tenderness, abdominal pain, polydipsia, polyuria	Nausea, flank pain, abdominal pain and tenderness
Peak blood pressure (mmHg)	160/100	152/100	182/94
Peak creatinine (mg/dL)	2.3	5.4	10.64
Lowest eGFR	36.4	13.1	5.9
Renal biopsy results	AIN and ATN with normal glomeruli	AIN with normal glomeruli	ATN with normal glomeruli

*Described by Koshy et al.[20]
†Described by Thorsteinsdottir et al.[21]
‡Patient described in this review.
AIN, acute interstitial nephritis; ATN, acute tubular necrosis; eGFR, estimate glomerular filtration rate.

The exact mechanism of renal insult in this patient cannot be determined given the number of ingredients contained in N.O.-Xplode and the lack of information regarding quantities of each ingredient within the proprietary blend. The previous cases associating N.O.-Xplode with side effects or organ dysfunction focused on nitric oxide and its precursors, L-arginine and arginine α-ketoglutarate, because of their vasodilatory effects and effect on hemodynamics.[7,8] While supplemental nitric oxide may have caused palpitations, headache, and ischemic colitis in previous cases, it probably cannot be blamed for renal failure. Rather, nitric oxide is thought to be renally protective. In the setting of systemic increases in nitric oxide and L-arginine, both the afferent and efferent arterioles of the kidney dilate, leading to an actual increase in GFR.[9,10]

It is beyond the scope of this discussion to examine each ingredient in the proprietary blend of N.O.-Xplode; however, creatine is of special interest because of its widespread use and the availability of safety data.[11] Randomized, placebo-controlled studies demonstrate no renal dysfunction in association with up to 7 days of creatine supplementation.[12–14] However, the patient in this case took N.O.-Xplode for several months. The available data examining long-term creatine use shows no deleterious effect on renal function but are somewhat limited by lack of randomization.[15–19] In 2 of the largest studies, the treatment groups were volunteers already taking creatine supplementation before the trials according to their own dosage preferences. Expert panels have interpreted this body of evidence to mean that creatine does not negatively affect renal function and is generally safe for use by healthy individuals.[11] However, there are 2 published reports of cases that are extremely similar to our patient and do associate creatine with acute renal failure.[20,21]

In the previous cases, young healthy men taking creatine presented with flank and/or abdominal pain, elevated blood pressure, and elevated creatinine. Table 1 compares patient characteristics and their disease courses. In the 2 previously published cases, renal function returned to normal after stopping the creatine supplement, and renal biopsies showed acute interstitial nephritis and/or tubular injury with normal glomeruli. In these 2 previous cases and our patient, the renal injury was nonoliguric and associated with only mild electrolyte disturbances. The similarities between these 3 patients are striking; however, our patient had by far the most significant decrease in eGFR.

Perhaps this case of renal failure was due to long-term creatine supplementation in the form of N.O.-Xplode, or perhaps it was caused by one of the many other ingredients in the dietary supplement's proprietary blend, a patient-specific drug metabolism problem, or an underlying predisposition to renal dysfunction. Ultimately, the unknowns involved in this case make it impossible to know exactly why the patient developed renal failure, but they do demonstrate the deep-rooted problems with dietary supplement use. As is com-

mon, the patient had not consulted a health care provider before initiating use of this dietary supplement, and information regarding the exact amount of each ingredient, including creatine, contained in the proprietary blend are not available, making deduction of the pathophysiology of organ dysfunction and comparison to previous cases difficult. Most important, the lack of safety assurance data makes it difficult to determine whether this is likely to happen to other patients.

It is critical that family physicians are able and open to counseling patients on the inherent risks associated with dietary supplements because of their lack of Food and Drug Administration regulation, unknown efficacy, and possible serious adverse outcomes, as this case highlights.

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