Consequence of patient substitution of nattokinase for warfarin after aortic valve replacement with a mechanical prosthesis

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This report describes a patient's self-substitution of nattokinase for the vitamin K antagonist warfarin after aortic valve replacement with a mechanical prosthesis. Nattokinase is an enzyme derived from a popular fermented soybean preparation in Japan (natto), which has fibrinolytic properties and is gaining popularity in nontraditional health journals and nonmedical health websites as an over-the-counter thrombolytic. After nearly a year of use of nattokinase without warfarin, the patient developed thrombus on the mechanical valve and underwent successful repeat valve replacement. We believe this is the first documented case of nattokinase being used as a substitute for warfarin after valve replacement, and we strongly discourage its use for this purpose.

Oral anticoagulation with vitamin K antagonists such as warfarin has been the usual standard of care following mechanical cardiac valve replacement. The fear of increased bleeding risk while taking warfarin has prompted some patients to self-adjust their dosing of anticoagulation or to stop therapy completely. Another subset of patients has sought nontraditional medicines to decrease or replace conventional anticoagulation regimens. We describe a patient's self-substitution of nattokinase for warfarin following replacement of the aortic valve with a mechanical prosthesis.

CASE REPORT

A 53-year-old man was admitted to our hospital with dyspnea and mild chest pain. Three years earlier, his stenotic bicuspid aortic valve was replaced with a 25 mm St. Jude mechanical prosthesis. His perioperative course was uneventful, and he returned to work at his busy chiropractic practice. His extracurricular hobbies included strenuous physical activities such as distance running. Approximately 12 months prior to his current presentation, he discontinued his warfarin and began to supplement his diet with 100 mg of nattokinase per day, a dose recommended by an alternative health journal for thrombolysis. The patient first noticed a change in his health about 6 weeks prior to seeking medical attention when he started to get more dyspneic when running. The dyspnea was reproducible when walking 2 blocks and further progressed to dyspnea at rest.

On examination, he did not appear in distress. His lungs were clear to auscultation, and precordial exam revealed a soft, mechanical S2, a 2/6-crescendo/decrescendo systolic murmur and an early diastolic murmur. Two-dimensional transthoracic echocardiogram disclosed at least moderate aortic regurgitation. Transesophageal echocardiogram suggested mechanical disc restriction with both aortic insufficiency and stenosis. Fluoroscopic evaluation of the mechanical prosthesis showed severe restriction of disc mobility. At reoperation, extensive fibrin and thrombus accumulation was present on both the aortic and ventricular sides of both discs. The clotted valve was removed and replaced with a 23 mm Carbomedics Top Hat valve. His postoperative course was uncomplicated. Prior to surgery the patient had agreed to continue using warfarin alone as his oral anticoagulant.

DISCUSSION

Natto is a traditional Japanese food derived from boiling or steaming soybeans and fermenting them with the bacteria *Bacillus subtilis*. It became a part of the Japanese culture late in the Edo period (1600–1868), particularly in the eastern Kanto region of Japan. During this time, the soybeans were packed in straw and buried underground for a week or more, coming into contact with the naturally occurring bacillus found in the straw. This combination resulted in soybean fermentation.

Natto is available in Japan but is difficult to find in most other countries. In 1987, Sumi et al found that natto contains a potent fibrinolytic enzyme that they coined nattokinase (1), and an oral form is now available to consumers worldwide as a supplement without a physician's prescription. This 275 amino acid has similar sequences to other natural endogenous enzymes. Sumi et al claimed that it closely resembles plasmin and strongly hydrolyzes fibrin. It is also suggested that nattokinase has been the most potent fibrinolytic enzyme among 200 foods investigated for oral fibrinolytic therapy (2). Subsequently, there has been some preliminary evidence of thrombolysis in rats

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(3, 4) and evidence of complete dissolution of arterial thrombi within 5 hours of oral administration of nattokinase in dogs (5). However, the authors of this case report have found limited data on the anticoagulation properties of natto and nattokinase in human subjects (6–8). Thrombin activity has been found to be increased following thrombolysis, which in turn may have paradoxically increased our patient's risk of valve thrombosis (9, 10). Further studies of nattokinase, recently conducted by Yongjun et al, have given promising insight into the development of mutant strains with improved catalytic efficiency by shuffling DNA from homologous genes of *Bacillus* species (11). No viable alternatives to warfarin have been found for mechanical heart valves. As a matter of fact, the direct thrombin inhibitor dabigatran was found to be unacceptable and the trial stopped early in favor of warfarin.

1. Sumi H, Hamada H, Tsushima H, Mihara H, Muraki H. A novel fibrinolytic enzyme (nattokinase) in the vegetable cheese Natto; a typical and popular soybean food in the Japanese diet. *Experientia* 1987;43(10):1110–1111.
2. Sumi H, Taya N, Nakajima N, Hiratani H. Structure and fibrinolytic properties of nattokinase. *Fibrinolysis* 1992;6(Suppl 2):86.
3. Fujita M, Hong K, Ito Y, Fujii R, Kariya K, Nishimuro S. Thrombolytic effect of nattokinase on a chemically induced thrombosis model in rat. *Biol Pharm Bull* 1995;18(10):1387–1391.
4. Suzuki Y, Kondo K, Matsumoto Y, Zhao BQ, Otsuguro K, Maeda T, Tsukamoto Y, Urano T, Umemura K. Dietary supplementation of fermented soybean, natto, suppresses intimal thickening and modulates the lysis of mural thrombi after endothelial injury in rat femoral artery. *Life Sci* 2003;73(10):1289–1298.
5. Sumi H, Hamada H, Nakanishi K, Hiratani H. Enhancement of the fibrinolytic activity in plasma by oral administration of nattokinase. *Acta Haematol* 1990;84(3):139–143.
6. Homma K, Wakana N, Suzuki Y, Nukui M, Daimatsu T, Tanaka E, Tanaka K, Koga Y, Nakajima Y, Nakazawa H. Treatment of natto, a fermented soybean preparation, to prevent excessive plasma vitamin K concentrations in patients taking warfarin. *J Nutr Sci Vitaminol (Tokyo)* 2006;52(5):297–301.
7. Hsia CH, Shen MC, Lin JS, Wen YK, Hwang KL, Cham TM, Yang NC. Nattokinase decreases plasma levels of fibrinogen, factor VII, and factor VIII in human subjects. *Nutr Res* 2009;29(3):190–196.
8. Cesarone MR, Belcaro G, Nicolaides AN, Ricci A, Geroulakos G, Ippolito E, Brandolini R, Vinciguerra G, Dugall M, Griffin M, Ruffini I, Acerbi G, Corsi M, Riordan NH, Stuard S, Bavera P, Di Renzo A, Kenyon J, Errichi BM. Prevention of venous thrombosis in long-haul flights with Flite Tabs: the LONFLIT-FLITE randomized, controlled trial. *Angiology* 2003;54(5):531–539.
9. Merlini PA, Bauer KA, Oltrona L, Ardissino D, Spinola A, Cattaneo M, Broccolino M, Mannucci PM, Rosenberg RD. Thrombin generation and activity during thrombolysis and concomitant heparin therapy in patients with acute myocardial infarction. *J Am Coll Cardiol* 1995;25(1):203–209.
10. Granger CB, Becker R, Tracy RP, Califf RM, Topol EJ, Pieper KS, Ross AM, Roth S, Lambrew C, Bovill EG. Thrombin generation, inhibition and clinical outcomes in patients with acute myocardial infarction treated with thrombolytic therapy and heparin: results from the GUSTO-I Trial. GUSTO-I Hemostasis Substudy Group. Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries. *J Am Coll Cardiol* 1998;31(3):497–505.
11. Yongjun C, Wei B, Shujun J, Meizhi W, Yan J, Yan Y, Zhongliang Z, Goulin Z. Directed evolution improves the fibrinolytic activity of nattokinase from Bacillus natto. *FEMS Microbiol Lett* 2011;325(2):155–161.