

Table
Provocation test with vitamin B₁₂^a

Dilution	Amount, mL	Route
1:100	0.1	Subcutaneous
1:10	0.1	Subcutaneous
Neat	0.1	Subcutaneous
Neat	1	Intramuscular

^aThe interval from administration (injection) of the dilution to the allergologic evaluation was 15 minutes.

wheel and a 7-mm diameter erythema. Because an intradermal test with saline caused a wheal with a diameter of 2 mm and a 3-mm diameter erythema, the skin test result was not considered to be clearly positive, and a provocation test with hydroxycobalamin was performed. Thirty minutes after the last dose, the patient developed urticaria but no angioedema, arterial hypotension, or wheezing. Methylprednisolone and chlorpyramine were administered, and the urticaria resolved. Prick, intradermal, and provocation tests were performed with cyanocobalamin, and all the results were negative. Neither of the preparations of vitamin B₁₂ that we used contained benzyl alcohol.

The patient later received cyanocobalamin on 4 occasions under our observation, without any sign of an allergic reaction. The treatment with cyanocobalamin was continued. During the next 12 months, no allergic reactions occurred.

The described allergic reaction was immediate but confined to the skin without respiratory or cardiovascular involvement. Our patient had a history of urticaria to hydroxycobalamin 17 years beforehand; however, the result of the first provocation test, performed in March 2010, was negative, and he tolerated the vitamin for some time before urticaria appeared again. As highlighted in the position paper on drug provocation tests published by the European Academy of Allergology and Clinical Immunology, if the interval from the reaction to allergologic evaluation is too long, the drug provocation test can yield a false-negative result.⁸ Therefore, in the case of a positive history of drug allergy and negative skin and provocation test results, allergists may decide to repeat testing after 2 to 4 weeks.⁸

Because our patient in 2010 at first tolerated hydroxycobalamin and urticaria appeared after the eighth dose of the vitamin, indicating that repeated contact with the vitamin was necessary for resensitization, the described reaction is likely an IgE-mediated immediate allergic reaction.

Anaphylactic shock due to SonoVue

SonoVue (Bracco, Milan, Italy), a second-generation contrast agent, is a suspension of phospholipid-stabilized sulfur hexafluoride (SF₆) microbubbles.¹ When SonoVue is used in ultrasonography to enhance the echogenicity of blood, it improves the signal-to-noise ratio. It is only used when the results of imaging tests performed without the use of a contrast agent are inconclusive. It can be used for scanning the heart chambers, large blood vessels, and lesions in the breast and the liver.

We present the case of a 39-year-old woman who had liver cirrhosis of unknown cause (Child-Pugh score B) and portal hypertension and had experienced an episode of upper gastrointestinal tract bleeding secondary to esophageal varices. She experienced anaphylactic shock after administration of SonoVue.

In most reported cases of vitamin B₁₂ allergy, skin tests (prick and intradermal) with cobalamin were performed. We also performed provocation tests because the intradermal test result was equivocal, and both reactions, in 1993 and in 2010, were not severe.

Reactions to cyanocobalamin^{1,2,4} and hydroxycobalamin^{3,4,6,7} have been reported. Patients allergic to hydroxycobalamin can have positive intradermal test results to both compounds, possibly because of cross-reactivity.^{6,7} In other cases, intradermal test results were positive only with the suspected compound and negative with the alternate compound.^{1,3}

We conclude that in cases of immediate allergic reactions to vitamin B₁₂, an allergologic evaluation consisting of prick, intradermal, and sometimes provocation tests is needed to determine whether hydroxycobalamin or cyanocobalamin can be safely used for future supplementation.

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In July 2011, the patient was admitted to the hospital for a focal liver lesion. She underwent contrast-enhanced abdominal ultrasonography with SonoVue. Immediately after the patient received an intravenous bolus injection of 2 mL of SonoVue, she experienced heat sensation in the upper trunk and neck, throat tightness, extensive skin erythema, dyspnea, cyanosis, and loss of consciousness. She also exhibited hypotension (blood pressure, 50/30 mm Hg), tachycardia, and silent chest, and her Glasgow Coma Scale score was 7. The patient was admitted to the intensive care unit, where she was intubated; received mechanical ventilation; and was immediately administered intravenous fluids, corticosteroids, and antihistamines. Because there was no improvement in hypotension, drip administration of norepinephrine was started. Five hours later, the patient's signs and

symptoms began to improve, and she was extubated. She was maintained under observation in the intensive care unit for 24 hours. The tryptase level was not analyzed at this point. Subsequently, the patient was admitted to the Gastroenterology Service.

Three months after the patient was discharged, she was examined in the Allergy Department. Once she signed the informed consent form, skin prick tests and intradermal tests were performed with SonoVue, beginning with a dilute solution (1/10,000) to prevent a severe allergic reaction; the concentration was increased by 10-fold every 15 minutes until the concentration of the undiluted dose (5 mg/mL) was reached. All the skin test results were negative. The patient's basal tryptase level was 3.74 kU/L. A challenge test was not performed because the authors did not think that the risk of anaphylaxis was justified.

Considering that this was the first time that the patient had been administered SonoVue, the subsequent signs and symptoms of anaphylaxis and the results of the skin prick and intradermal tests indicated non-IgE-mediated anaphylactic shock. Similar adverse reactions to SonoVue have been previously reported.²

Although the mechanism underlying these adverse reactions to SonoVue remains unclear, we believe that it is highly likely to correspond to the mechanisms underlying anaphylactoid reactions, such as adverse reactions to contrast media. We therefore hypothesize that the underlying mechanism could be the result of direct mast cell activation, complement activation, inhibition of platelet aggregation accompanied by increased serotonin release, and inhibition of enzymes such as cholinesterase.³

During postmarketing surveillance, rare cases suggestive of hypersensitivity, including anaphylactic shock, have been reported. Nineteen other serious nonfatal adverse events (AEs) have been reported, 18 of which were anaphylactoid or vasovagal reactions, as defined by the reporting physician. Of these 19 serious AEs, 9 were cardiac events (bradycardia, 4 cases; tachycardia, 2 cases; and myocardial ischemia, 3 cases). Eleven of these 19 patients received SonoVue for echocardiography. Resuscitation, where required, was always successful.⁴

Only a few articles are available on AEs associated with SonoVue use. In a recently published article, Geleijnse et al⁵ analyzed 352 consecutive SonoVue echo-contrast studies with respect to the AEs that occurred in 274 patients during a 4-year period. They found that during these studies, 7 patients (2.0%) experienced AEs, 4 patients (1.1%) experienced mild allergic reactions that led to skin erythema and mild sinus tachycardia, and 3 patients (0.9%) experienced a severe allergic reaction that resulted in nonfatal shock.⁵

Despite the adverse reactions reported, SonoVue appears to have a good safety profile. However, the rates of adverse reactions due to SonoVue seem comparable to or lower than the rates of adverse reactions that result from the use of other imaging modalities, and the clinical benefit-to-risk ratio appears favorable for SonoVue. However, physicians should be aware of the possibility of serious adverse reactions, similar to the one presented in this case, and treat them as soon as possible.

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Intraoperative anaphylaxis induced by the gelatin component of thrombin-soaked gelfoam in a pediatric patient

Intraoperative anaphylaxis is relatively rare, with an estimated incidence of 1:25,000 to 1:4,000.¹ A 2½-year-old girl with a history of tetralogy of Fallot status post repair underwent tethered spinal cord repair in a latex-free environment. She was orally premedicated with midazolam and ketamine and received intraoperative fentanyl, sevoflurane, etomidate, dexamethasone, cefazolin, and a crystalloid infusion (lactated Ringer's). Two and a half hours later, thrombin-soaked Gelfoam was applied on the dura, and her wound was irrigated with 50,000 units of bacitracin solution. Within 2 to 3 minutes, she developed generalized urticaria, a drop in her systolic blood pressure from 110 to 50 mmHg, and a decrease of her oxygen saturation from 99% to 90% with marked difficulty in ventilation. She responded quickly to immediate high-pressure manual ventilation, albuterol, diphenhydramine, intravenous fluids, and ephedrine, which was readily available for instant use.

After the allergy service was consulted, it was revealed postoperatively that a few months prior the patient developed generalized hives, lip swelling, and abdominal pain 20 minutes after ingesting Spam, which is canned pork meat with a characteristic gelatinous

glaze, also known as aspic. Her condition required epinephrine administration in an outside emergency room. She had since tolerated pork, milk, egg, wheat, seafood, peanut, and tree nuts and had not eaten soy.

Gelfoam is an absorbable gelatin sponge intended for application to bleeding surfaces as a hemostatic agent and prepared from purified pork skin gelatin. It can be used alone or in combination with topical thrombin. For this patient, given that the thrombin-soaked Gelfoam and Spam have porcine gelatin as a common ingredient, it was highly suspected that the antigen inducing these 2 anaphylactic reactions was gelatin.

Patient under skin-prick testing was performed on the back to histamine (Hollister-Stier, Spokane, Washington; 6 mg/mL histamine base, 10 mg/mL histamine dihydrochloride), preservative-free porcine gelatin (College Pharmacy, Colorado Springs, Colorado), full-strength bacitracin solution (1,000 units/mL), MMR-II (Merck Pharmaceuticals, full-strength solution, containing 14.5 mg of hydrolyzed porcine gelatin per dose), soy (Greer Laboratories, Lenoir, North Carolina), and normal saline (0.9%). She was positive to gelatin (wheal 15, flare 40) and histamine