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A Case Report of Cardiac Arrest After Intravenous Administration of Sulfur Hexafluoride (Lumason®) Ultrasound Enhancing Agent

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Abstract

Ultrasound enhancing agents (UEAs) are medications that enable clear visualization of ultrasound images. While large studies have demonstrated the safety of these agents, case reports of life-threatening reactions temporally associated with their use have been published and reported to the Food and Drug Administration. Current literature describes the most serious adverse reactions due to UEAs to be allergic in nature; however, embolic phenomena may play a role as well. Here, we report a case of unexplained cardiac arrest following the administration of sulfur hexafluoride (Lumason®) in an adult inpatient undergoing echocardiography where resuscitative efforts were ultimately unsuccessful, and review possible mechanisms of cardiac arrest based on prior published literature.

Keywords

cardiac contrast, cardiac arrest, sulfur hexafluoride

Introduction

Ultrasound enhancing agents (UEAs) enable clear visualization of the cardiac chambers in situations where ultrasound imaging is technically difficult due to patient-specific factors such as obesity or extensive lung disease. The 3 commercially available UEAs in the United States include Optison® (perflutren protein-type A microspheres, approved 1995), Definity® (perflutren lipid microspheres, approved 2001), and Lumason® (sulfur hexafluoride lipid-type A microspheres, approved 2014).

In 2007, the safety of UEAs was questioned after the Food and Drug Administration (FDA) received numerous reports of death and severe cardiopulmonary reactions temporally associated with UEA use.[1] The FDA instated an UEA Black Box Warning (BBW) labeling the potential for serious cardiopulmonary reactions, contraindications that included any severe cardiac or pulmonary disease, and a required 30-minute monitoring period after administration. Subsequently, FDA-mandated safety studies that evaluated unenhanced vs enhanced echocardiography in various patient populations did not find a signal for increased risk of serious adverse events or deaths associated with UEA use.

The BBW was softened in 2011 to remove the blanket monitoring period and stated that serious cardiopulmonary reactions may occur but are uncommon.[1] Of note, the majority of these studies evaluated Definity® or Optison®, as Lumason® was unavailable until 2014. However, Lumason® has been marketed in Europe as Sonovue® since the early 2000s, and large retrospective analyses encompassing over 50,000 patients reported an overall serious adverse events rate of <0.01% with Sonovue®. Nevertheless, case reports of serious adverse events temporally associated with UEA administration do exist, which should warrant provider caution with use. Here we report a case of sudden cardiac arrest following the administration of Lumason® for echocardiography enhancement.

Case Report

A 35-year old male was admitted to our institution by his neurologist for treatment of a probable multiple sclerosis (MS) exacerbation. The patient reported that 2 weeks prior to

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admission while ambulating with his walker, he suddenly became unable to walk and fell to the ground. Since then, he developed worsening bilateral leg weakness to the extent that he was bedbound and could ambulate only with assistance. He also reported paroxysmal chills and the development of bilateral lower extremity edema. His past medical history included MS diagnosed 8 years prior, morbid obesity (weight 161.5 kg, body mass index 48.2 kg/m^2), legal blindness due to optic atrophy, chronic lower back pain, myelopathy, bowel and bladder dysfunction, and gall stones. Mobitz type 1 second degree atrioventricular block was also listed as part of his past medical history. The patient had no known allergies to medications or other substances. He had previously been prescribed interferon beta and glatiramer for MS treatment but was no longer taking either. He reported to only be using medical marijuana prior to his hospitalization.

On the day of admission, all labs were normal except for a urinalysis concerning for a possible urinary tract infection (UTI). An electrocardiogram (EKG) showed normal sinus rhythm with no QRS, QTc, or PR interval abnormalities. Magnetic resonance imaging (MRI) of the spine was obtained which appeared stable from prior studies, although there was noted motion artifact. A brain MRI was attempted but aborted due to extreme back pain while lying flat. The patient was initiated on methylprednisolone sodium succinate 1000 mg intravenously (IV) daily for presumed MS exacerbation, ceftriaxone 1 g IV daily for empiric UTI treatment, and enoxaparin 40 mg subcutaneously (SQ) daily for venous thromboembolism (VTE) prophylaxis.

The next day, no labs were drawn other than a routine blood glucose. A bilateral lower extremity duplex was done, which appeared to be negative, although some veins were poorly visualized due to edema. To continue workup for his bilateral lower extremity edema, a transthoracic echocardiogram (TTE) was requested. Due to poor visualization of the cardiac chambers, Lumason® 2 mL IV bolus was ordered and administered through a new peripheral venous line. Just prior to administration of the UEA, the patient was noted to be at his baseline–he was joking with staff and had no complaints. Immediately following administration, the patient reported feeling flushed and "felt like something was wrong." He then became unresponsive and pulseless. Cardiopulmonary resuscitation was initiated for pulseless electrical activity (PEA) and the patient was intubated. No angioedema was encountered upon intubation and no mucocutaneous manifestations of anaphylaxis were evident. An automated chest compression device was utilized to improve quality of chest compressions in the setting of large body weight. During the arrest, the patient received medications including epinephrine, sodium bicarbonate, dextrose, calcium, magnesium, dexamethasone, and tissue plasminogen activator. After approximately 45 minutes of resuscitative efforts, the patient, still pulseless, was placed on veno-arterial extracorporeal membrane oxygenation (VA ECMO). He developed ventricular fibrillation that converted to a slow sinus rhythm after defibrillation and receipt of amiodarone. His post-arrest troponin was 1.29 ng/mL. A transesophageal echocardiogram (TEE) was obtained with normal biventricular function and no pulmonary embolism, aortic dissection, or pericardial effusion. Despite maximal support on VA ECMO and inopressors, the patient developed worsening lactic acidosis and died several hours later. Autopsy was not performed.

Discussion

The use of UEAs for echocardiography with suboptimal visualization is a practice recommended by the 2018 American Society of Echocardiography Guidelines because of the value they may bring to improve outcomes related to early diagnosis of disease.[2] The guidelines reference over 20 studies that compared unenhanced vs enhanced echocardiography in patient populations that included outpatients, inpatients, and those with critical illness, pulmonary hypertension, or undergoing stress echocardiography.[1,2] The results of these studies were remarkably similar, demonstrating no signal for increased risk of short or long-term adverse events or mortality in patients receiving UEAs. Collectively, adverse event rates were <1%, with serious events occurring in <0.01% of recipients.

While Lumason® was underrepresented in the FDA safety studies, data from Europe evaluating sulfur hexafluoride under the brand name of Sonovue® have also demonstrated very low complication rates.[3-7] Nevertheless, serious and life-threatening reactions from UEAs have been published, with the etiology of events appearing to be allergic or embolic in nature.[1] Some authors suggest that due to the history of the UEA BBW, "pseudocomplications" related to UEA use may be overly reported, but these events may be attributable to progression of underlying disease.[8] Causality is often difficult to determine. In the patient case we describe, the Naranjo adverse drug reaction probability scale yielded a score of 3, indicating possible likelihood of a drug-induced adverse event.[9] No alternative etiologies of cardiac arrest could be determined, and no medications other than Lumason® were administered within hours of the event. Lumason® was reconstituted and administered according to package labeling by the patient's bedside nurse, who did not note any anomalies during this process. The patient had no clinical indications that he would experience such a catastrophic reaction to Lumason®.

Ultrasound Enhancing Agents have most commonly been associated with a type-1 hypersensitivity reaction called Complement Activation-Related Pseudoallergy (CARPA). This is a non-IgE-mediated allergic reaction that most commonly occurs after a bolus of UEA is administered, and is more likely in females and those with atopic history.[1] More recently, IgE-mediated hypersensitivity reactions to polyethylene glycol (PEG), present in both Lumason® and Definity®, have been reported.[10-12] In response to an alert from

MedWatch, the FDA's safety reporting system, the American Society of Echocardiography and the European Association of Cardiovascular Imaging published consensus statements addressing the risk of hypersensitivity to PEG.[13,14] While they did not suggest any additional monitoring or lab testing necessary for patients receiving Lumason® or Definity®, they did recommend counseling patients on the possibility of a severe adverse reaction (1 in 10,000) and avoiding use in those with known allergies to PEG or PEG-containing laxatives. The FDA prescribing information for both Lumason® and Definity® was also updated to include PEG allergy as a contraindication.[13,14]

Several case reports of anaphylactic reactions to UEAs have been published to date, however it does not appear that these reactions are more common than those with intravascular contrast media used in radiology.[3,6,10] Olson et al reported a case of an anaphylactic cardiac arrest after administration of Lumason® in a patient with systemic mastocytosis, who regained pulse after epinephrine and bag-valve-mask ventilation.[15] In a review of adverse reactions related to Sonovue® after administration for 352 cardiac studies, Geleijnse et al detailed 3 cases of anaphylactic shock in patients with no atopic history. All patients responded to corticosteroids, antihistamines, and epinephrine.[6] Similarly, in a review of 463,434 administrations of sulfur hexafluoride for contrast-enhanced ultrasound for various indications, Shang et al reported 14 severe, non-fatal anaphylactic reactions necessitating treatment.[16] Anaphylaxis to the PEG component of Definity® and Sonovue® has also been reported and confirmed with intradermal skin testing in 2 case reports.[10,11] In 2022, two medical centers reported an increase in the incidence of allergic adverse reactions to UEAs after the onset of the COVID-19 vaccination program, suggesting possible PEG sensitization after widespread exposure to the PEGylated mRNA vaccines.[12] Lastly, Kuzma et al published an abstract of anaphylactic shock following Lumason® administration requiring intubation and vasopressors. Three days after the anaphylactic episode, the patient developed an acute ischemic stroke with brain MRI confirming numerous embolic infarcts. Etiology of infarcts were thought to be microembolisms from Lumason®.[17] In our patient case, anaphylaxis as the etiology of cardiac arrest was thought to be unlikely due to receipt of prior pulse steroids (methylprednisolone 1000 mg) and failure of resuscitative efforts with intubation and epinephrine. The absence of angioedema upon intubation, rash, or urticaria also suggests against anaphylaxis as the cause of arrest. However, in this patient, systemic embolism as the etiology could not be ruled out.

Embolic-type adverse reactions due to UEAs have also been hypothesized due to the agents' chemical structures. In a retrospective review of Sonovue® studies for abdominal imaging, Piscaglia et al described a patient with atherosclerotic vasculopathy who had a renal artery stent placed for ostial stenosis. Two weeks after placement, the patient underwent a Sonovue® imaging study to assess for in-stent restenosis. After Sonovue® administration, the patient became severely hypotensive, erythematous, endorsed clouding of consciousness and severe dorsolumbar pain. Anti-allergic therapies were administered. Contrast-enhanced CT demonstrated complete stent occlusion. It was unclear whether the acute dorsolumbar pain suggested an acute embolic occlusion related to Sonovue®.[3] Of note, UEAs have been reported to cause back/flank pain related to microbubble retention in the renal cortex from complement-mediated interactions with the glomerular microvascular endothelium.[18] Alternative case reports suggesting embolic phenomena have also been described. Kontzialis et al published a report of a patient who developed an acute ischemic stroke 3 minutes after administration of Lumason® for stress echocardiography. Brain CT confirmed fat lobules within the sulci, and tissue plasminogen activator was administered with resolution of symptoms.[19] Lastly, Grecu et al published 2 cases of activation of the VA ECMO system bubble/thrombus detector alarm after administration of Definity®. In an effort to prevent cardiovascular or neurologic events associated with embolism, this ECMO safety feature may lead to total pump shutdown. The alarm is activated in the presence of bubbles or microthrombi >5 mm in dimension.[20] These reports raise concern for large UEA-associated embolisms.

Ultrasound enhancing agents are composed of a fluorocarbon gas encapsulated by an outer protein or phospholipid shell that helps mimic the rheology of circulating red blood cells. Less than 5% of the microspheres are noted to be larger in size than a red blood cell. Within 2 minutes after injection, 80% of the gas is exhaled, and the naturally occurring phospholipids are dispersed into the body's own fat deposits.[1] Based on the structure of the compound, it is possible that either the sulfur hexafluoride gas or the phospholipid shell may coalesce and create a fluorocarbon-based gas embolism or phospholipid-based fat embolism, respectively. In our patient, echocardiography after ECMO cannulation displayed normal biventricular function. However, it is possible that receipt of tissue plasminogen activator and/or use of ECMO support may have acutely improved right heart mechanics. At this time, a causal relationship is unable to be determined.

Conclusion

While UEAs have demonstrated an excellent safety profile in large registry studies, there are rare reports of severe and fatal adverse events. Here, we reviewed a case of fatal cardiac arrest following administration of sulfur hexafluoride. Use of sulfur hexafluoride should be done in a setting with resuscitative capabilities which includes readily available emergency medications, equipment, and personnel trained in Advanced Cardiovascular Life Support (ACLS). Allergic and embolic etiologies should be addressed in the case of a life-threatening reaction or cardiac arrest.

Declaration of Conflicting Interests

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