

Expert Consensus Statement from the American Society of Echocardiography on Hypersensitivity Reactions to Ultrasound Enhancing Agents in Patients with Allergy to Polyethylene Glycol



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The American Society of Echocardiography is composed of health care providers and scientists committed to the well-being of patients through excellence in cardiovascular imaging. In alignment with the society's mission to provide education that improves clinical outcomes, this consensus statement has been generated to provide our members and all practitioners of echocardiography with information and recommendations that will benefit the safety of patients receiving ultrasound enhancing agents (UEAs). Specifically, this document provides expert opinion on the clinical impact of the recent alert from MedWatch, the US Food and Drug Administration (FDA) product safety reporting system, on presumed type I immediate hypersensitivity reactions to the polyethylene glycol (PEG) component of UEAs.

The UEAs that are approved for use by the FDA include perfluorocarbon or sulfur hexafluoride microbubbles stabilized with "shells" composed of albumin or lipid.¹ These agents can interact with immune cells of the monocytic/phagocytic system via opsonization involving the complement (C') system or interaction with specific immune cell surface receptors.² These interactions contribute to the normal and uneventful mechanism for clearance of UEAs from the circulation by the reticuloendothelial (mononuclear phagocyte) system. Serious immune-related reactions to UEAs are rare and have been attributed largely to C' activation-related pseudoallergy reactions, which are known to also occur with liposomal drug prepa-

rations.^{1,3-6} The lipid-based UEAs approved for human use by the FDA contain PEG either in the excipient (vehicle or inactive ingredient) alone (Lumason and SonoVue; Bracco Diagnostics, Milan, Italy) or in the microbubble shell and the lipid excipient (Definity, Definity RT, and Luminity; Lantheus Medical Imaging, North Billerica, MA). The PEG components not only stabilize the agents but when incorporated in the shell can also reduce microbubble opsonization and interaction with cells.⁷ The potential for rare immunoglobulin E-mediated type I hypersensitivity reactions to PEG components has been recently recognized after publication of case reports implicating PEG allergy.^{8,9} The MedWatch alert is based on post-marketing pharmacovigilance from more than two decades that identified 11 cases of anaphylaxis, including two deaths, related to the administration of UEAs in patients with preexisting PEG hypersensitivity.

The comments below provide expert opinion on the impact of newly recognized PEG hypersensitivity. We believe that it is important to recognize the potential for reactions to the PEG component of lipid UEAs. Our recommendations also take into account that these reactions remain extremely rare and that UEAs provide vital information that improves patient outcomes arising from the ability of UEAs to detect or exclude life-threatening conditions or to stratify patients to lifesaving therapies.¹

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KEY BACKGROUND INFORMATION

- PEG is also known as macrogol or polyoxyethylene. It is a polyether compound that is commonly used in a multimeric form (H-IO-CH²-CH²Iⁿ-OH) with designation according to its molecular weight (e.g. PEG-5000, which contains 113 ethylene glycol repeats).
- PEG is a component (excipient) in thousands of enteral and parenteral drugs, including commonly used medications in cardiovascular medicine. It is also a component in coronavirus vaccines that are based on messenger ribonucleic acid technology and is present in many skin creams, cosmetics, and household products.
- Although rare, PEG allergy is established in the scientific literature.^{10,11} It is unknown how often allergies to the thousands of drugs that contain PEG occur from immunoglobulin E-mediated reaction to the active drug versus reactions to excipients including PEG. The most commonly used agents that contain solely PEG as an active ingredient are certain bowel preparations used before colonoscopy and certain laxatives containing PEG or macrogol.

Abbreviations**FDA** = US Food and Drug Administration**PEG** = Polyethylene glycol**UEA** = Ultrasound enhancing agent

- Of the FDA-approved UEAs, only lipid-based agents (Definity, Definity RT, Luminity, Lumason, and SonoVue) contain PEG or PEGylated lipids.
- For Definity preparations and Luminity, PEG is a component of an amphiphilic “PEGylated” phospholipid (DPPE-PEG-5000) that becomes incorporated in the lipid monolayer shell and represents 8%

molar fraction of all lipid content in the vial. The amount of DPPE-PEG-5000 per vial is 0.304 mg for Definity and 1.52 mg for Definity RT. For Lumason and SonoVue, PEG-4000 is in the excipient and is not incorporated into the shell. The amount of PEG-4000 per vial of Lumason is 24.56 mg.

- The MedWatch alert refers to 11 cases presumed to be type I immediate hypersensitivity reactions to PEG on the basis that they occurred in patients with known PEG hypersensitivity. The alert does not provide confirmatory data, such as subsequent hypersensitivity testing, that are helpful for confirming that these events were immunoglobulin E–mediated reactions to PEG.
- The period over which these presumed PEG-related anaphylactic reactions occurred has not yet been publicly reported. However, the alert was the result of pharmacovigilance programs that span several decades. It appears that these cases accumulated over 10 years, resulting in an incidence of reported reactions at less than one per million doses of lipid-stabilized UEA administered. Because reactions are reported on a voluntary basis, it is not always possible to reliably estimate the true frequency or their causal relationship to UEAs.
- In the absence of postreaction specialized testing by experts in allergy and immunology, the clinical differentiation of C' activation–related pseudoallergy and type I hypersensitivity reactions is extremely difficult.
- The treatment of severe C' activation–related hypersensitivity and type I hypersensitivity reactions is similar and includes epinephrine, steroids, antihistamines, bronchodilators, and other supportive measures. The alert from the FDA does not indicate that any changes in therapy or monitoring for severe reactions to UEAs should be enacted.
- Before the MedWatch alert, package inserts for the lipid-based UEAs had already cautioned against their use in patients with hypersensitivity to any of the components of the agent. The package inserts for the relevant UEAs have been updated to specifically caution against their use in patients with hypersensitivity reactions to PEG.

RECOMMENDATIONS FOR LABORATORY POLICIES ON UEAS

1. The MedWatch alert provides additional insight into mechanisms by which serious reactions to lipid-based UEAs can occur; it does not change the known incidence of these reactions, which occur in approximately one in every 10,000 administrations,^{3,4} making UEAs among the safest contrast agents used in medical imaging. Accordingly, we do not recommend any changes to laboratory policy with respect to indications for their use. In other words, UEAs have an extremely low risk-to-benefit ratio, and their use should be continued in situations in which they have been shown to be effective.¹
2. Lipid-based UEAs (Definity, Definity RT, Luminity, Lumason, and SonoVue) are contraindicated in patients who have had known or suspected hypersensitivity to these UEAs or their components (established recommendation); they are also contraindicated in patients with known hypersensitivity to PEG (new recommendation). Because patients may be unaware of products that contain PEG, health care providers should inquire about hypersensitivity to agents that contain PEG or macrogol as their

active ingredient, including certain bowel preparations used for colonoscopy and laxatives.

3. Recommendations for counseling patients on the frequency of severe reactions (one in 10,000) should not change.
4. All sonographers, nurses, and physicians who routinely administer UEAs should be trained in the recognition of hypersensitivity reactions; cardiopulmonary resuscitation equipment must be readily available for use by trained personnel (established recommendation).
5. The FDA alert does not contain any information that would justify changes in laboratory policy for patient monitoring or treatment algorithms for hypersensitivity reactions.

SUMMARY

- The FDA alert enhances our understanding of the mechanism of severe reactions to UEAs. The known incidence of these reactions remains low and unchanged (one in 10,000 administrations). Because the risk-to-benefit ratio for UEAs remains extremely low, we do not recommend any changes to laboratory policy regarding indications for their use. The use of these agents should continue in situations where they have been shown to be effective.
- Lipid-based UEAs (Definity and Lumason) are contraindicated in patients who have histories of prior hypersensitivity to these UEAs, to PEG (macrogol), or to PEG-containing products such as certain bowel preparations for colonoscopy or laxatives.

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