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Ultrasound contrast agent hypersensitivity in patients allergic to polyethylene glycol: position statement by the European Association of Cardiovascular Imaging

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The Food and Drug Administration alert enhances our understanding of the mechanism of severe reactions to ultrasound-enhancing agents (UEAs). The known incidence of these reactions remains low and unchanged (1 in 10 000 administrations). Because the risk-to-benefit ratio for ultrasound contrast agents (UCAs) remains extremely low, we do not advise 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 impactful. Lipid-based UCAs (SonoVue and Luminity) are contraindicated in patients who have a history of prior hypersensitivity to these UEAs, to polyethylene glycol (PEG) (macrogol), or to PEG-containing products, such as certain bowel preps for colonoscopy or laxatives.

Keywords ultrasound contrast agent • hypersensitivity • position statement • EACVI

This statement is in response to a recent alert by MedWatch, a product safety reporting body of the US Food and Drug Administration (FDA) regarding possible Type I immediate hypersensitivity to polyethylene glycol (PEG) present in lipid-based ultrasound contrast agents (UCAs) also known as ultrasound-enhancing agents (UEAs). These UCAs are approved by the FDA and European Medicine Agency (EMA) for clinical use. PEG is a part of lipid-based UCA as a constituent of the shell of Luminity, Lantheus Medical Imaging (known as Definity in the USA) and it is also present as an excipient (vehicle) in SonoVue, Bracco Diagnostics (known as Lumason in the USA). PEG stabilizes these lipid-based microbubbles either to facilitate the production of stable microbubbles or to allow longer persistence in the circulation.[1] PEG is not present in the protein-based UCA, Optison, and GE healthcare. PEG is an adjuvant in many topical enteral and parenteral drugs, including cardiovascular medicines, mRNA-based COVID-19 vaccines, and skin creams, cosmetics, and household products.

Although very rare, PEG allergy is known to occur.[2] The rarity of serious allergic reactions maybe be gauged by the very rare occurrence of anaphylaxis after mRNA vaccine administration, which contains high concentrations of PEG, in 2–5 cases in a million. The very low event of hypersensitivity reactions with UCA in <1 in 10 000 also suggests a very low prevalence of any type of hypersensitivity, including serious allergies with PEG. Allergies with UCA are mostly ascribed to complement activation-related pseudoallergy (CARPA).[3] However, PEG allergy is thought to be IgE-mediated. Both CARPA and IgE-mediated anaphylaxis are treated similarly with epinephrine, steroids, and antihistamines.[4]

UCAs are approved both by FDA and EMA for clinical use and endorsed by both European and American guidelines as Class 1 agents for the diagnosis of various cardiac conditions.[5,6] UCA's provide crucial information that translates into improved patient outcomes based on its ability to detect or exclude life-threatening conditions and to direct physicians to administer life-saving therapies.[4,5] In most cases, where UCA are indicated the benefits of UCA far outweigh the very low serious adverse events <1 in 10 000 administration observed with UCA. The new information on PEG allergy derived from historical data collected over

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2 decades as part of pharmacovigilance required to be conducted by the companies by the regulatory authorities as part of safety measure does not alter the extremely low event rates seen with UCA consistently over these 2 decades. Thirteen cases of anaphylaxis were reported including two deaths which translates into one in a million event following use of UCA over this period. However, the correct incidence may be underestimated as these are voluntarily reported but at the same time the anaphylaxis maybe due to other causes.

(1) Recommendations are already present for lipid-based UCAs (Luminity and SonoVue also known as Definity and Lumason, respectively in the USA) regarding contraindication in patients who have had a known or suspected hypersensitivity to these UCAs or their components.
(2) PEG is a component of SonoVue and Luminity. Accordingly, they are also contraindicated in patients with known hypersensitivity to PEG.
(3) Patients may be unaware of products that contain PEG, thus, healthcare providers should inquire about hypersensitivity to agents that contain PEG or macrogol as their active ingredient including certain bowel preparations prior to colonoscopy and laxatives. Medications, such as epinephrine, beta2-agonists, antihistaminic drugs, and methylprednisone, should also be available to treat potential adverse reaction when UCAs are used.

European Association of Cardiovascular Imaging (EACVI) agrees with the summary published by American Society of Echocardiography (ASE)[7] as depicted below but very slightly modified to reflect European practice.

Conflict of interest: none declared.

References

1. Fisher NG, Christiansen JP, Klibanov A, Taylor RP, Kaul S, Lindner JR. Influence of microbubble surface charge on capillary transit and myocardial contrast enhancement. *J Am Coll Cardiol* 2002;**40**:811–9.
2. Krantz MS, Liu Y, Phillips EJ, Stone CA Jr. Anaphylaxis to PEGylated liposomal echocardiogram contrast in a patient with IgE-mediated macrogol allergy. *J Allergy Clin Immunol Pract* 2020;**8**:1416–1419.e3.
3. Szebeni J. Complement activation-related pseudoallergy: a new class of drug-induced acute immune toxicity. *Toxicology* 2005;**216**:106–21.
4. Cosyns B, Pasquet A, Van Camp G, Hernot S, Droogmans S, Unger P *et al.*; Belgian Working Group on Non-Invasive Cardiac Imaging. Safety of ultrasound contrast agents: "Primum non nocere"? *Acta Cardiol* 2009;**64**:547–52.
5. Senior R, Becher H, Monaghan M, Agati L, Zamorano J, Vanoverschelde JL *et al.* Clinical practice of contrast echocardiography: recommendation by the European Association of Cardiovascular Imaging (EACV) 2017. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1205.
6. Porter TR, Mulvagh SL, Abdelmoneim SS, Becher H, Belcik JT, Bierig M *et al.* Clinical applications of ultrasonic enhancing agents in echocardiography: 2018 American Society of Echocardiography Guidelines Update. *J Am Soc Echocardiogr* 2018;**31**:241–74.
7. Lindner RJ, Belcik JT, Main ML, Montarano A, Mulvagh SL, Olson J *et al.* Expert consensus statement from the American Society of Echocardiography on hypersensitivity reactions to ultrasound enhancing agents in patients with allergy to polyethylene glycol. J Am Soc Echocardiogr 2021. :S0894-7317(21)00471-5. doi: 10.1016/j.echo.2021.05.002