AIUM CEUS Expert Task Force Support of Established Safety Record of Ultrasound Contrast Agents and Continued Use Where Medically Appropriate

The American Institute of Ultrasound in Medicine (AIUM) is a multidisciplinary organization devoted to the safe and effective use of medical diagnostic and therapeutic ultrasound. In keeping with our ongoing commitment to patient safety, we recognize the importance of the recent U.S. Food and Drug Administration (FDA) efforts to communicate the potential risk of administering ultrasound contrast agents (UCAs) in patients who are sensitive to polyethylene glycol (PEG), along with the modifications to product labeling. Reactions to PEG, although extremely rare, need to be considered alongside the clear benefits of contrast-enhanced ultrasound (CEUS). To this end, the AIUM provides the following brief summary and recommendations.

Impact of CEUS in Patient Care

Ultrasound contrast agents are ultrasound-specific imaging agents that are used routinely around the world for a variety of indications. Ultrasound contrast agents are injected intravenously as a reliable method of detecting heart disease and stratifying a patient's risk of heart attack or stroke. Intravenous use of UCAs is also used to identify and characterize tumors of the liver, kidney, prostate, breast, and other organ systems, assess vessels, and to monitor the effectiveness of cancer therapies, in adults and children. Ultrasound contrast agents can also be injected directly into the urinary system to detect problems with the kidneys and bladder.

The low cost, portability, and widespread availability of ultrasound equipment allows for CEUS imaging in a variety of clinical settings, including in the clinic or at a patient's bedside. Contrast-enhanced ultrasound images are produced in real time with high resolution, often exceeding resolution of images obtained with computed tomography (CT) or magnetic resonance imaging (MRI). Thus, a targeted and reliable CEUS scan can reduce unnecessary downstream tests that may be more expensive or invasive, and present their own safety risks. The reduction of downstream testing may, in turn, lower overall imaging costs, expedite the patient's diagnosis and treatment, and improve hospital workflows.

Safety Record of CEUS

Ultrasound contrast agents are expelled from the body within minutes. There is no known cross-reactivity with CT or MRI contrast agents and can be used in patients with renal insufficiency or renal failure. Decades of experience, with the administration of millions of doses of UCAs throughout the world including in the U.S.A., along with an extensive body of published safety data, show that UCAs are exceedingly safe for the overwhelming majority of patients. In fact, peer-reviewed published scientific data show that UCAs save the lives of critically ill patients, reducing mortality by 24% compared to patients who did not have the benefit of CEUS imaging. Ultrasound contrast agents are particularly important for pediatric imaging, allowing providers to avoid modalities that use ionizing radiation (radiography or CT) or may require sedation or anesthesia (MRI).

PEG-related considerations

Polyethylene glycol is a component in thousands of enteral (oral) and parenteral (eg, intravenous) drugs, including many commonly used over-the-counter medications such as laxatives. Polyethylene glycol is also a component of COVID-19 vaccines based on mRNA technology and is present in many skin creams, cosmetics, and household products. In fact, PEG is commonly

attached to other compounds, drugs, or contrast agents to improve their safety and efficacy a process called PEGylation. PEGylated molecules are often less toxic, less antigenic and immunogenic, and highly water-soluble, improving their clinical utility. In addition, PEGylation further increases the therapeutic longevity and half-life of the PEGylated drugs and reduces dose frequency by preventing excessive excretion of drugs. FDA-approved PEGylated drugs have been used in a wide variety of clinical applications, such as treatment of cancer, chronic kidney diseases, hepatitis, multiple sclerosis, hemophilia, and gastrointestinal disorders, since 1990 when the first PEGylated protein approved by the U.S. FDA entered the market.

Although rare, PEG allergy is established in the scientific literature. It is unknown how often allergies to the thousands of drugs that contain PEG occur from IgE-mediated reaction to the active drug versus reactions to excipients including PEG (1,2). The most commonly used agents that contain solely PEG as an active ingredient are certain bowel preps used prior to colonoscopy and certain laxatives containing PEG or macrogol.

Conclusions and Recommendations

The FDA alert points out the potential severe reaction to patients with a known PEG allergy. The known incidence of these reactions remains extremely low and unchanged (1 in 10,000 administrations). Because the risk of severe allergic reactions to UCAs remain extremely low, and they provide very substantial benefits to our patients, we do not recommend any changes to clinical policy regarding indications for their use. The new labeling highlights a concern that was already implied in the original labeling and is based on data obtained over a decade with no new or changed data. The use of UCAs should continue in appropriate clinical situations under supervision with the addition of specifically asking patient if they have a PEG allergy.

Facilities using lipid-based UCAs (Definity and Lumason) should question patients if they have a history of prior hypersensitivity to these UCAs, to PEG (macrogol) in particular, or to PEG-containing products such as certain bowel preps for colonoscopy or laxatives. The use of UCAs should be considered contraindicated in these patients.

The AIUM joins the International Contrast Ultrasound Society (ICUS) and the American Society of Echocardiography (ASE) in supporting this recommendation.

REFERENCES

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