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Safety of Ultrasound Contrast Agents in the Pediatric Oncologic Population: A Single-Institution Experience

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Abstract

OBJECTIVE—Little information is available regarding the safety of ultrasound contrast agents in children. The purpose of this article was to assess the safety profile of the IV administration of ultrasound contrast agents in the pediatric oncology population.

MATERIALS AND METHODS—Patients with pediatric solid malignancies who were enrolled on institutional clinical trials conducted between June 2003 and January 2013 and who met our institutional screening criteria for contrast-enhanced ultrasound (CEUS) were eligible. After providing informed consent or assent for CEUS, subjects received IV bolus injections of one of two contrast agents for imaging of the primary tumor or a metastatic target lesion. Hemodynamic parameters, including heart rate, cardiac rhythm, and oxygen saturation, were monitored immediately before and for 30 minutes after the administration of the contrast agent. Interviews with the subject or a guardian were conducted by the principal investigator or a radiologist coinvestigator before and after the examination to assess for any adverse effects.

RESULTS—Thirty-four subjects (21 male and 13 female) ranging in age from 8 months to 20.7 years (median, 8.7 years) underwent 134 CEUS. No detrimental change in hemodynamic status occurred in any subject. Three subjects (3/134, 2.2%) reported mild transient side effects on one occasion each, two (2/134, 1.5%) had taste alteration, and one (1/134, 0.8%) reported mild transient tinnitus and lightheadedness. These reactions did not recur in these subjects on subsequent CEUS examinations.

CONCLUSION—The IV administration of ultrasound contrast agents is safe and well tolerated in the pediatric oncology population. Further studies in children are needed to confirm our findings.

Keywords

contrast-enhanced ultrasound; pediatric solid malignancy; safety; ultrasound

The pediatric population may be more sensitive than the adult population to the effects of ionizing radiation associated with medical imaging, and in particular CT [1, 2]. Given the

evolving knowledge of the potential carcinogenic effects associated with medical radiation, methods that do not deliver ionizing radiation, such as MRI and ultrasound, should be optimized and used whenever possible in the pediatric population. Contrast-enhanced ultrasound (CEUS) holds promise in many pediatric applications, including in the diagnosis of acute appendicitis [3], assessment of solid organ injury after trauma [4], and detection of vesicoureteral reflux [5–10]. Other applications are on the horizon [11, 12], including the assessment of blood flow in solid malignancies [13, 14].

Although widely used in adult echocardiography [15–21] and frequently in adult hepatic imaging applications [22–29], little information is available regarding the use of contrast-enhanced ultrasound in children and, in particular, the pediatric oncologic population. Although the feasibility of CEUS in the pediatric oncologic population has been reported [30], little safety data have been published.

At present, two ultrasound contrast agents are approved by the Food and Drug Administration (FDA) for use in adult cardiology patients. These microspheres consist of perfluorocarbon gas (perflutren, Optison [package insert, GE Healthcare]) surrounded by an outer shell of protein or phospholipid [31]. After injection, these agents remain within the vascular space and appear highly reflective on ultrasound [30]. Because these contrast agents remain intravascular, they are uniquely suited for use as a surrogate marker of blood flow. At our institution, we have used CEUS to assess solid tumor blood flow and response to chemotherapy and antiangiogenic therapy in several therapeutic trials. Because these contrast agents have not been FDA approved for use in children, we implemented a rigorous screening and monitoring policy for CEUS. The purpose of this study was to review our experience and assess the safety profile of the IV administration of these agents in pediatric patients with solid malignancies.

Materials and Methods

Study Cohort

Patients with solid malignancies who were enrolled on one of four institutional protocols between June 2003 and January 2013 were eligible candidates for CEUS examinations. The protocols included OPTUS [30], a safety and efficacy study of Optison (perflutren protein-type A microspheres, GE Healthcare) ultrasound contrast agent in children with solid abdominal and pelvic malignancies, and three therapeutic trials: NB05, a single-arm phase II study of gefitinib and irinotecan in children with high-risk neuroblastoma [32]; ANGIO1, a phase I study of bevacizumab and sorafenib combined with low-dose cyclophosphamide in patients with refractory solid tumors and leukemia [33]; and RET05, a protocol for the study and treatment of patients with intraocular retinoblastoma [34]. All protocols were institutional research board approved and HIPAA compliant, and all subjects or their guardians signed informed consent or assent for CEUS as appropriate. The results of the OPTUS study and the CEUS findings of a subset of ANGIO1 subjects have been previously published [30, 33].

Prescreening, Eligibility Requirements, Injection Technique, and Monitoring

After subjects were enrolled, they were pre-screened before undergoing CEUS. Institutional contraindications to CEUS are shown in Appendix 1. These criteria are stricter than the contraindications currently listed in the Optison package insert but were developed during the time of the black-box warning by the FDA for ultrasound contrast agents. These restrictions were applied to all our research subjects, and this was continued for the duration of the study for consistency. All subjects were required to undergo 12-lead ECG and echocardiography within 90 days before CEUS to assess for underlying cardiac abnormalities, pulmonary hypertension, and right-to-left cardiac shunting. In addition, physical examination and history were required to rule out other preexisting contraindications. Screening unenhanced ultrasound of the primary tumor or target metastatic lesion was required to ensure that the tumor was visible by ultrasound. Subjects meeting these inclusion criteria and who were enrolled on treatment protocols underwent CEUS before initiation of therapy and at treatment-protocol-specified time points during therapy.

All subjects enrolled on research protocols received Optison contrast material. Optison is an injectable suspension of human serum albumin microspheres encapsulating octafluoropropane gas with a mean particle size of 2.0–4.5 μm and a mean pulmonary elimination half-life of 1.3 minutes. Two nonprotocol subjects received Definity (perflutren liquid microspheres, Lantheus) contrast material, which is composed of lipid microspheres, ranging in size from 1.1 to 3.3 μm , encapsulating octafluoropropane gas with a mean half-life of 1.3 minutes. One of the two subjects receiving Definity was undergoing standard-of-care cancer therapy and the other was a patient who underwent CEUS to evaluate for possible recurrence of adrenal neuroblastoma versus postoperative hematoma. Subjects enrolled on the OPTUS protocol received escalating doses of Optison on the basis of body surface area beginning at a very low dose of 0.125 mL/m² and escalating in 0.075 mL/m² increments to 0.350 mL/m²; injected doses ranged from 0.07 mL to 0.73 mL (mean, 0.37 mL). Our current institutional practice for ultrasound contrast dosing is based on the available pediatric contrast ultrasound literature. Subjects weighing less than 20 kg receive 0.3 mL and those weighing 20 kg or more receive 0.5 mL [35]. All subjects were imaged with a Sequoia ultrasound scanner (Acuson) using a 4V2-, 8C2-, or 6C2-MHz transducer for unenhanced imaging and a 6C2- or 15L8-MHz transducer for contrast-enhanced imaging (selected for maximum image resolution by the sonographer and principal investigator). The Cadence Contrast Agent Imaging contrast pulse sequence software program (Acuson) was used for all contrast-enhanced imaging. For purposes of our study, at the pretreatment baseline evaluation, the tumor of interest had to enhance at least 5 dB after the administration of the contrast agent. If the tumor did not enhance 5 dB at the initial contrast dose, the dose was doubled and the injection repeated after waiting at least 10 minutes for the first dose to be metabolized. If the tumor did not enhance at least 5 dB after the second higher dose, the subject was not eligible to be followed with CEUS and no further CEUS examinations were performed.

All subjects were monitored by the sedation nursing staff with continuous pulse oximetry and three-lead ECG (Propaq monitor, Welch-Allen) before, during, and for 30 minutes after

the injection of contrast agent. Subjects were required to have an oxygen saturation of at least 92% on room air immediately before contrast administration. The contrast agent was delivered through indwelling central venous catheters in all but one subject who preferred peripheral IV access. The first 13 subjects, who were enrolled on the OPTUS protocol, received bolus injections using a power injector at a rate that was tailored during that study [30]. Subsequently, for ease of administration, we hand injected the contrast agent followed by a bolus of normal saline. Either the radiologist principal investigator or a radiologist coinvestigator administered the contrast agent. These investigators assessed the subjects for any additional physical changes or symptoms, by conducting patient or guardian interviews before and immediately after the injections.

Results

Forty subjects were screened. Three did not undergo CEUS because the tumor of interest was not adequately visualized by ultrasound (one middle mediastinal mass, one pleural-based pulmonary nodule, and one skull lesion partially obscured by overlying bone). Two subjects had sonographically visible tumors but declined CEUS. One subject did not undergo CEUS because of oxygen saturations below 92% on room air just before the scheduled examination. Two subjects had tumors that did not enhance the required 5 dB even after doubling the initial dose (one retinoblastoma and one middle mediastinal mass). Therefore, there were 34 subjects who met the inclusion criteria and underwent a total of 134 CEUS examinations. One hundred twenty-six examinations were performed with Optison and eight with Definity. There were 21 males and 13 females with a median age of 8.7 years (range, 0.7–20.8 years). Primary diagnoses were neuroblastoma ($n = 9$); rhabdoid tumor ($n = 6$); rhabdomyosarcoma ($n = 4$); hepatocellular carcinoma ($n = 3$); Wilms tumor ($n = 3$); synovial sarcoma ($n = 2$); and hepatoblastoma, Ewing sarcoma, osteosarcoma, epithelial sarcoma, transitional cell carcinoma, retinoblastoma, and renal cell carcinoma ($n = 1$ each). Forty contrast injections were administered at the time of primary diagnosis or relapse but before initiation of therapy, and 94 were performed while subjects were undergoing chemotherapy. There were no clinically significant changes in heart rate, cardiac rhythm, or oxygen saturation in any subject. Three subjects (3/134, 2.2%), all of whom received Optison, reported mild transient effects; two (2/134, 1.5%) had altered taste and one (1/134, 0.8%) reported mild tinnitus and lightheadedness on one occasion each. These reactions did not recur on follow-up CEUS examinations in these subjects. The radiologist investigators did not witness any adverse reaction that could be attributed to the administration of the contrast agent in the very young subjects who were unable to verbalize a reaction nor did their guardians voice concern that their child had experienced an adverse reaction.

Discussion

We performed careful hemodynamic monitoring of 34 children and young adults who underwent 134 CEUS examinations with the IV administration of an ultrasound contrast agent. Our subjects all had underlying pediatric malignancies that were newly diagnosed or they had undergone one or more courses of chemotherapy before CEUS. Despite these underlying illnesses and the toxic effects of chemotherapy, none of our subjects had any

detrimental change in heart rate, cardiac rhythm, or oxygen saturation after the administration of the ultrasound contrast agent. We also performed interviews with the subjects before and after CEUS when feasible, depending on the subject's age. Three subjects (3/134, 2%) reported minor transient reactions immediately after the injection of Optison on one occasion each. These same subjects did not experience any side effects during or after numerous follow-up CEUS examinations. This rate is much lower than the 15% we previously reported for this patient population, likely due to our larger sample size [30]. In our current study, two subjects (2/134, 1.5%) reported altered taste, a reaction that has been previously reported to occur in 2% (4/203) of adults and 5% (1/20) of children receiving Optison [16, 35]. It is possible that taste alteration is due to the heparinized saline flush used to deliver the bolus of contrast agent rather than the contrast agent itself. One of our subjects (1/134, 0.8%) reported tinnitus and lightheadedness, which are also known rare side effects of Optison administration [package insert, GE Healthcare].

Because ultrasound contrast agents have not been FDA approved for pediatric use and because these agents carry a boxed warning, they have not been widely used in children. The FDA boxed warning was issued in 2007 in response to the deaths of four patients and approximately 190 other serious cardiopulmonary reactions that were temporally but not clearly causally related to the administration of Definity in adults undergoing echocardiography. The warning stated that ultrasound contrast agents were contraindicated in patients with significant cardiovascular compromise (acute cardiopulmonary syndromes, QT prolongation, severe pulmonary hypertension, or acute decompensated heart failure) and recommended that all patients be monitored for 30 minutes after the administration of the agent. Because of these requirements, many centers halted the use of ultrasound contrast agents, and there was a strong rebuttal from the cardiology community. Numerous large retrospective studies were undertaken to compare the morbidity and mortality associated with contrast-enhanced echocardiography to unenhanced echocardiography in adults. In 2009, Main et al. [36] summarized the results of seven of these studies that included 188,748 adults. The studies objectively confirmed that there was no increased risk of morbidity or mortality in adults undergoing contrast-enhanced echocardiography, including patients with severe underlying cardiopulmonary disease. On the basis of these findings, the boxed warning was revised in 2008 to remove the contraindications regarding underlying cardiopulmonary disease, and the recommendation to monitor patients for 30 minutes after contrast administration was dropped [36]. Because of the theoretic risk of microemboli resulting from microspheres bypassing the pulmonary circulation, history of right-to-left, bidirectional, or transient right-to-left cardiac shunt remains in place as a contraindication. However, this has recently been challenged by an article stating the position of the International Contrast Ultrasound Society (ICUS) board [37]. In this article, the ICUS board recommends removal of this contraindication because there is no scientific evidence to support it. The ICUS board also pointed out that right-to-left shunts are not a contraindication to the administration of radioactive macroaggregated albumin, which consists of larger particles than ultrasound contrast agent microspheres.

Although numerous studies have investigated the safety profile of ultrasound contrast agents in adults, much less is known of the safety of these agents in children. Our findings add to the body of literature regarding the safety of the IV use of these agents in children and are

consistent with prior reports. In 2012 Riccabona [38] reported the results of a large European survey investigating the safety of the intravesical and IV use of SonoVue (sulfur hexafluoride, Bracco) ultrasound contrast agent in children. SonoVue is the most commonly used ultrasound contrast agent in Europe. It is similar to Definity and Optison but is composed of a phospholipid shell encasing sulfur hexafluoride gas. The survey included the safety findings of 948 IV applications of SonoVue in children 0–18 years old (mean age, 5 years) that were performed for a variety of indications, including trauma and oncology. There were six (6/948, 0.6%) minor adverse reactions in five subjects. These included altered taste in three (3/948, 0.3%), urticaria or rash in two (2/948, 0.2%), and hyperventilation in one (1/948, 0.1%). One adolescent subject, who was an oncology patient older than 18 years and therefore not included in the survey results, had a severe anaphylactic reaction necessitating resuscitation. This patient had received numerous, repeated SonoVue administrations and had other known allergies [38].

Most serious adverse events occurring after administration of imaging contrast agents are anaphylactic reactions. The rate of severe anaphylactic reactions after the administration of perflutren microspheres is approximately 1:7000 (0.014%), which is much lower than the reported rate of 35–95:100,000 (0.035–0.095%) for iodinated contrast agents [11, 17, 36, 39–41]. According to the most recent *American College of Radiology Manual on Contrast Media* (version 9) [42], the rate of severe anaphylactic reactions associated with gadolinium-based contrast agents is comparable to ultrasound contrast agents and is very low at 0.001–0.01%. An added benefit of ultrasound contrast agents is that, unlike iodinated and gadolinium-based agents, they are not contraindicated in patients with renal disease nor do they induce renal insufficiency or nephrogenic systemic fibrosis [42].

A limitation of our study is the somewhat moderate sample size. Additional pediatric studies are needed to confirm our findings. Another minor limitation was the inability of our youngest subjects to verbalize the occurrence of adverse side effects. Therefore, in studies such as ours that include very young children, the true incidence of minor adverse reactions may be underestimated. However, in our study, a radiologist investigator was present in the examination room during all contrast injections and therefore was able to directly assess the subject's reaction to the contrast agent. No obvious reactions were witnessed that could be attributed to the administration of the contrast agent in our youngest subjects.

In conclusion, we found that IV-administered ultrasound contrast agents have an excellent safety profile in children and may be superior to other commonly used imaging contrast agents. In addition, this modality is an attractive alternative to CT and MRI for a number of other reasons. Perhaps the most important is the lack of ionizing radiation with the use of ultrasound. CT exposes the patient to ionizing radiation, a known potential carcinogen, with effects that are stochastic and increase with the amount and frequency of exposure. This point is especially relevant to the pediatric oncology population because these children undergo numerous CT examinations during disease treatment and after completion of therapy. Additionally, many children require sedation for MRI, but CEUS can be performed quickly and easily without sedation and at a lower cost. A limitation of ultrasound in general as well as in our study is that not all anatomic disease sites are amenable to visualization with ultrasound and image quality is operator dependent. Even so, numerous applications

other than oncology have been proposed for the use of CEUS in children, including assessment of solid organ injury after trauma, characterization of liver and renal masses, and assessment of inflammatory bowel diseases such as Crohn disease [11]. Our data support the safety of CEUS for these applications in children.

The relationship between the contrast agent and the imaging software program is important to consider when determining the dose of ultrasound contrast agents [43]. In the future, improvements in contrast imaging software may allow the use of lower contrast agent doses. Currently, we continue to screen patients to assess for contraindications to ultrasound contrast agents at our institution, but we no longer require monitoring of patients after the administration of these agents. We recently added Optison to our institutional formulary for use as clinically indicated.

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APPENDIX 1: Contraindications to Contrast-Enhanced Ultrasound Performed for Research Purposes at Our Institution

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- Worsening or clinically unstable congestive heart failure
 - Acute myocardial infarction or acute coronary syndromes
 - Serious ventricular arrhythmias or high risk for arrhythmias due to prolongation of the QT interval
 - Respiratory failure manifested by signs or symptoms of carbon dioxide retention or hypoxemia
 - Severe emphysema, pulmonary emboli, or other conditions that cause pulmonary hypertension due to compromised pulmonary arterial vasculature
 - Hypersensitivity to perflutren
 - Pregnant
 - Lactating
 - Right-to-left, bidirectional, or transient right-to-left cardiac shunts
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