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● *Clinical Note*

SAFETY OF INTRAVENOUS APPLICATION OF SECOND-GENERATION ULTRASOUND CONTRAST AGENT IN CHILDREN: PROSPECTIVE ANALYSIS

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Abstract—The goal of the work described here was to assess the safety profile of intravenous second-generation ultrasound contrast agents (UCAs) containing sulfur hexafluoride in pediatric contrast-enhanced ultrasound. Between 2010 and 2013, a total of 167 examinations were performed in 137 children referred by the Oncology Department. Approval by an Independent Ethical Review Board on Scientific Research for the intravenous use of an UCA containing sulfur hexafluoride in children with oncologic diseases was obtained. Consent for UCA administration was acquired from the parents or legal guardians. Severe anaphylactic reaction was observed in 0.6% (n = 1). No other adverse events during or after intravenous administration of contrast were observed in the examined group (no changes in heart rate and rhythm, blood pressure, oxygen saturation or respiratory rate). There were no reports of subjective flushing, nausea, transient headaches or altered taste. Although second-generation ultrasound contrast agents are considered potentially safe, all investigators should be prepared for the development of adverse reactions and have provisions in place for all pediatric intravenous contrast-enhanced ultrasound examinations. More multicenter studies are essential to determination of an accurate UCA safety profile. (E-mail: mpiskunowicz@wp.pl)

Key Words: **Contrast-enhanced ultrasound, Children, Safety, Ultrasound, Ultrasound contrast agent, Adverse event.**

INTRODUCTION

The reduction of the risk associated with ionizing radiation used for diagnostic purposes is due largely to the development of ultrasound, which is the method of choice in many diagnostic guidelines. It appears that the use of second-generation contrast agents may allow the replacement of studies using ionizing radiation with ultrasound, especially in children with oncologic diseases.

Unfortunately, pediatric ultrasound with intravenous ultrasound contrast agents is still largely at the "research" stage (Claudon et al. 2013). Because of the lack of registration for use in patients under the age of 18, intravenous studies using second-generation ultrasound contrast agents are performed in a limited number of medical centers, with the consent of bioethics committees and the parents.

With respect to the safety profile of imaging studies, the risk of UCA side effects should be assessed and compared with those of iodinated contrast agents, computed tomography (CT) radiation exposure, gadolinium magnetic resonance imaging (MRI) contrast agents and the likelihood of patient sedation during MRI. It should be pointed out that the small number adverse reactions reported for second-generation contrast agents in adults does not mean they are safe to use in children (Darge et al. 2013; Morel et al. 2000; Piscaglia and Bolondi 2006). Unfortunately, so far the safety profile of UCAs in children is based on few publications describing individual adverse events (Coleman et al. 2014; Darge et al. 2013; McCarville et al. 2012; Piskunowicz et al. 2012; Riccabona 2012)

Here we describe our experience with the tolerability of intravenous administration of a second-generation contrast agent containing sulfur hexafluoride in patients under 18 y of age.

METHODS

The study included a group of pediatric patients from one hematologic oncology center. This prospective

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study began in December 2010 after receipt of approval by the Independent Ethical Review Board on Scientific Research of the Medical University in Gdansk to use an intravenous UCA containing sulfur hexafluoride in children with oncologic diseases. The examinations were performed using a Philips iU22 unit (Philips Medical Systems, Bothell, WA, USA) and the following probes: one convex probe (C5-1) and two linear probes (L5-17 and L9-3), adjusted to examinations using UCAs.

Inclusion criteria

The decision on a child's (age range: 0–18 y) qualification for intravenous contrast-enhanced ultrasound (CEUS) examination was always made in conjunction with the attending physicians. Children were included if there:

1. Failure to make a clear diagnosis after a previous imagining examination (CT, MRI), problems choosing the right diagnostic/therapeutic strategy.
2. Initial assessment and follow-up of patients with solid tumors before and during anti-neoplastic therapy.
3. Use of CEUS examination as an alternative to CT and MRI in the diagnosis or monitoring of suspicious proliferative changes.
4. Evaluation of residual disease after completion of anti-neoplastic therapy.
5. Assessment of adrenal gland lesions in children up to 1 y of age.
6. Monitoring of anti-neoplastic therapy complications.

Exclusion criteria

Children with the following problems were excluded from undergoing CEUS:

1. Heart defect found on echocardiography: any type of abnormality (performed in all patients).
2. Symptoms of active bacterial or viral infection and body temperature $>38.5°C$ (the next examination was scheduled after symptom resolution).
3. Lack of consent of the parents or legal guardian.
4. Uncertain pregnancy status.
5. Known sensitivity to sulfur hexafluoride or other components of UCA.

Safety provisions and methods of patient monitoring

To increase the tolerability of ultrasound examinations using an intravenous contrast agent, in accordance with the recommendations of the ethics committee, the research team included an anesthesiologist with experience in pediatric anesthesiology. The procedures performed by our team are as follows.

One day before the scheduled examination, the parents and the child met the physician who would be performing the examination, the anesthesiologist and the referring physician. The parent or guardian completed a questionnaire eliciting information on sensitivity to drugs and blood products, high blood pressure episodes, heart surgery and pregnancy status (in older girls).

On the day of the procedure, the child was admitted to the observation ward, where he or she remained for 24 h after the procedure. Blood pressure and heart rate monitoring, echocardiography and oxygen saturation measurements were performed for the duration of the examination and 30 min after its completion. Thirty minutes after the last administration of the UCA, a follow-up ultrasound was performed to determine the presence of UCA microbubbles in previously examined regions and/or large vessels (aorta, inferior vena cava, pulmonary vein).

The child was accompanied by one parent or legal guardian during the examination and while in the observation ward. Reactions to the UCA (local pain, nausea, vomiting or other) were recorded for the subsequent 30 min in the ultrasound department and for the subsequent 24-h period in the observation ward.

Medications

Sulfur hexafluoride (SonoVue, Bracco, Milan, Italy) was used for the ultrasound examination with UCA. Each milliliter of SonoVue contains 8 μL of the microbubbles (Cosgrove 2006; Greis 2004). The microbubbles are composed of sulfur hexafluoride gas (SF_6) surrounded by a stabilizing thin and flexible shell composed of phospholipids (Cosgrove 2006; Greis 2004). The microbubbles have a mean diameter of about 2.4 μm and easily pass through lung capillaries. Microbubbles undergo alternate, unequal contraction and expansion when exposed to the harmonic frequencies of an ultrasound wave. The beam is strongly reflected from the interface between the gas and the phospholipids and back to the transducer, creating the image (Cosgrove 2006; Greis 2004). The SonoVue suspension was prepared in accordance with the manufacturer's instructions.

The lack of sulfur hexafluoride reference doses for the pediatric population has created the need to establish a custom dosing regimen using the principle of minimum effective dose of contrast for a given body region examined. The volume of contrast agent administered was based on the patient's age and ranged from 0.1 to 1.8 mL.

RESULTS

In the period between December 2010 and December 2012, a total of 161 studies using ultrasound with an intravenous contrast agent containing sulfur hexafluoride were performed in 137 children (83 male, 54 female; mean age: 10.2 $\pm$ 6.0, range: 0–18 y) (Table 1, Figs. 1–3).