

● *Clinical Note*

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

MACIEJ PISKUNOWICZ,^{*} WOJCIECH KOSIAK,[†] TOMASZ BATKO,[†] ARKADIUSZ PIANKOWSKI,[‡]
KATARZYNA POŁCZYŃSKA,[†] and ELŻBIETA ADAMKIEWICZ-DROŻYŃSKA[†]

^{*}Department of Radiology, Medical University of Gdansk, Gdansk, Poland; [†]Department of Pediatric Hematology and Oncology, Medical University of Gdansk, Gdansk, Poland; and [‡]Department of Anesthesiology and Intensive Care, Medical University of Gdansk, Gdansk, Poland

(Received 8 May 2014; revised 5 November 2014; in final form 8 November 2014)

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) © 2015 World Federation for Ultrasound in Medicine & Biology.

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

Address correspondence to: Maciej Piskunowicz, Department of Radiology, Medical University of Gdansk, Debinki 7 St., 80-952 Gdansk, Poland. E-mail: mpiskunowicz@wp.pl

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 imaging 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 $>38.5^{\circ}\text{C}$ (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 ± 6.0 , range: 0–18 y) (Table 1, Figs. 1–3).

Table 1. Data on children who underwent contrast-enhanced ultrasound (n = 137)

Organ/body examined	Number of children	Number of examinations	Gender (male/female)	Age (y)*
Liver	39	48	26/13	9.7 ± 5.8
Testis	7	7	7/0	14.2 ± 4.5
Lymph nodes	13	13	6/7	14.4 ± 3.2
Chest	5	5	2/3	13.5 ± 5.2
Spleen	11	13	9/2	12.0 ± 5.7
Kidney(s)	19	29	12/7	8.1 ± 5.8
Soft tissue	7	7	4/3	11.4 ± 5.7
Adrenal gland(s)	8	9	6/2	5.3 ± 7.7
Other†	28	30	11/17	9.2 ± 5.7
Total	137	161	83/54	10.2 ± 6.0

* Mean ± standard deviation.

† Urinary bladder, periosteal changes, ovaries, intestines, retroperitoneal space, salivary glands, vessels.

One adverse event occurred after intravenous administration of an ultrasound contrast agent in the group of 137 patients. It was severe anaphylactic shock (potentially life-threatening) and was directly related to administration of the intravenous ultrasound contrast agent SonoVue.

Contrast-enhanced ultrasound examination was performed to monitor the effectiveness of therapy in an 11-y-old girl (weight: 28.5 kg, height: 138 cm) diagnosed with gastrointestinal stromal tumor of the stomach wall with liver metastases and was focused on the tumor. Forty-three seconds after intravenous administration of 0.6 mL SonoVue, the patient developed symptoms of anaphylactic shock. She began to report generalized pruritus and nausea. Systolic blood pressure decreased below 70 mm Hg and tachycardia up to 200 beats/min ensued. One minute later, the patient experienced bradycardia up to 45 beats/min and an O₂ saturation level of 60%. The preceding signs were accompanied by feelings of intense fear, without loss of consciousness. CEUS examination was immediately discontinued, and treatment was started. Oxygen, intravenous epinephrine and fluids (0.9% NaCl) were administered. After 2 h the

patient's general condition improved, and all symptoms resolved.

No other adverse events during or after intravenous administration of contrast were observed in the group (no changes in heart rate or rhythm, blood pressure, oxygen saturation or respiratory rate). There were no reports of subjective flushing, nausea, transient headaches or altered taste.

DISCUSSION

This article describes the initial experience of a single oncology center with the intravenous administration of second-generation intravenous ultrasound contrast agents in children. It includes the largest pediatric group for which a prospective evaluation of safety has been conducted to date.

Currently, apart from a few descriptions of single cases, only five original articles describing the results of CEUS after intravenous administration of contrast agent in a total of 165 children are available (Bonini *et al.* 2007; Coleman *et al.* 2014; Jacob *et al.* 2013; McMahon *et al.* 2005; Valentino *et al.* 2008) (Table 2). Three of the five articles report the use of sulfur hexafluoride without side effects (Bonini 2007; Jacob 2013; Valentino; 2008). In the other two studies, perfluorocarbon gas was used, and seven cases of side effects cases were reported (Coleman *et al.* 2014; McMahon *et al.* 2005). The article by McCarville *et al.* (2012) was omitted because of the sharing of data with latest work by Coleman *et al.* (2014).

In the adult population, the safety profiles of ultrasound contrast agents have been evaluated in a large population (Piscaglia and Bolondi 2006). Studies conducted on a group of 23,188 adults undergoing abdominal examination revealed 29 cases of adverse reactions related to SonoVue. Two of these cases were rated as severe, while the remaining 27 were non-life threatening; no fatalities were reported (Piscaglia and Bolondi 2006). The study confirmed that SonoVue has a favorable safety profile, with a rate of serious adverse reactions lower than

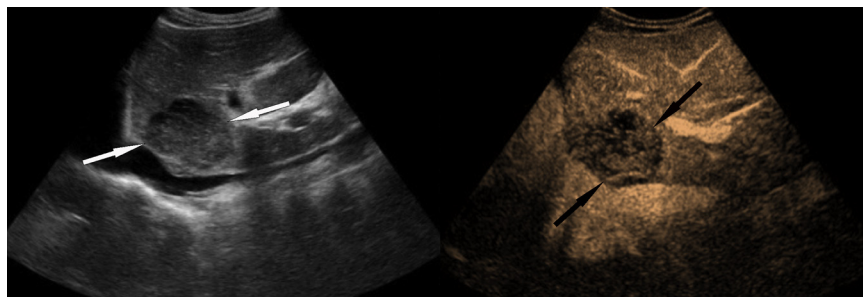


Fig. 1. Ten-year-old boy with NHL lesion in liver. White arrows on the B-mode image point to the lymphoma lesion in the liver. On the contrast-enhanced ultrasound image, the black arrows point to the same lesion.

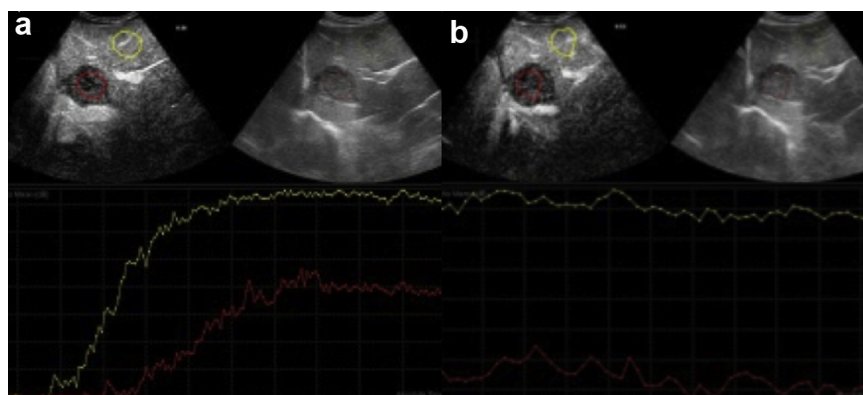


Fig. 2. Preliminary assessment of lymphoma lesion in liver (see Fig. 1). Initial examination and quantitative analysis of enhancement. (a) Red region of interest in the lesion, yellow region of interest in liver tissue. The curves below depict the intensity of the signal with time (0–30 s). (b) Red region of interest in the lesion, yellow region of interest in liver tissue. The curves below depict the intensity signal with time (46–60 s): fast washout.

1/10,000 patients (0.009%). In two prospective works, the authors used intravenous ultrasound contrast agents in individuals under 18 y of age and observed adverse reactions after their administration (Coleman et al. 2014; McMahon et al. 2005). In the study by Coleman et al. (2014), in which microspheres containing octafluoropropane gas were administered to 34 patients, 3 experienced mild adverse reactions, 2 had altered taste and 1 experienced mild tinnitus and lightheadedness on one occasion each. In a study of 20 children by McMahon et al. (2005), 4 experienced minor adverse reactions after administration of intravenous ultrasound contrast agent containing octafluoropropane. Three patients developed transient headache and one reported brief alteration of taste sensation.

Analysis of the published studies indicates a relatively large number of mild adverse reactions—up to 20% of patients in the study by McMahon et al. (2005). However, the majority of published studies using intravenous ultrasound contrast agents in children involved small groups of patients or individual cases, as a result of which, an objective assessment of tolerability and possible adverse reactions is not possible (Coleman et al. 2014; Darge et al. 2013; McMahon et al. 2005; Piskunowicz et al. 2012).

In our study, one severe complication occurred. Its course was similar to that of anaphylactic shock in adults

(Levano et al. 2012). To date, in addition to the 12 mild adverse reactions reported (Coleman et al. 2014; McMahon et al. 2005; Riccabona 2012), this is the only reported case of severe allergic reaction in a child after intravenous administration of a second-generation ultrasound contrast agent. There is a high probability that this reaction was caused by an allergen that activates complement (C), tentatively named C activation-related pseudo-allergy (CARPA) (Szebeni 2005). Although there is no known common underlying cause for most pseudo-allergies (reactions caused by radiocontrast media, non-steroidal anti-inflammatory drugs, analgesics, morphine and insect venoms), there is substantial evidence suggesting that the reactions caused by liposomes and micellar solvents have a common trigger mechanism: C activation (Szebeni 2005). SonoVue contains both potentially allergenic components (liposome, phospholipid shell) and solvents (Macrogol 4000, palmitic acid) that could cause severe allergic reactions. In these circumstances, the need to have rapid access to anti-anaphylactic drugs (particularly epinephrine) with each use of UCA, both in children and in adults, should be emphasized.

The dosing regimen presented in our study allowed us to obtain diagnostic images at a dose of contrast agent lower than that recommended in adults.

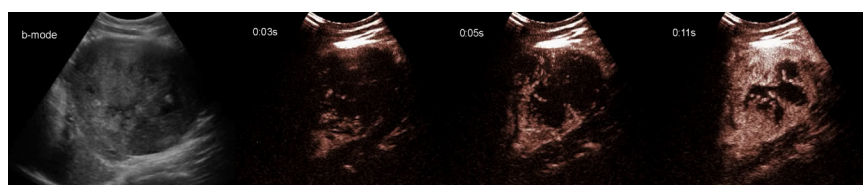


Fig. 3. Nine-year-old girl with a nephroblastoma. Images of lesion obtained in B-mode and contrast-enhanced ultrasound examinations.

Table 2. Doses and reported adverse events of intravenously administered ultrasound contrast agents in a pediatric population

Author	Number of children	Age (y)*	Contrast agent	Dose of contrast agent (mL)	Adverse events
McMahon <i>et al.</i> 2005	20	Median: 15 y (9–18)	Optison	<20 kg: 0.3 mL >20 kg: 0.5 mL	4 mild
Bonini <i>et al.</i> 2007	40	Mean: 2.0 y (2 mo–10 y)	SonoVue	0.5 mL (up to three injections)	None
Valentino <i>et al.</i> 2008	27	Mean: 8.9 y (4–13 y)	SonoVue	2 × 2.4 mL	None
Jacob <i>et al.</i> 2013	44	Median: 11.5 (4–18)	SonoVue	1.2–2.4 mL	None
Coleman <i>et al.</i> 2014	34	Median: 8.7 (8 mo–20.7 y)	Optison	0.07–0.73 mL or <20 kg: 0.3 mL >20 kg: 0.5 mL	3 mild
This work	137	Mean: 10.2 (0–18)	SonoVue	0.1–1.8 mL	1 severe

* Range given in parentheses.

CONCLUSIONS

The continued development of diagnostic methods using intravenous ultrasound contrast agents in children is limited by the lack of registration.

A significant restriction is the lack of uniform guidelines for monitoring patients under 18 y of age during and after the administration of intravenous ultrasound contrast agents. This is the reason it is difficult to analyze potential side effects and adverse reactions that occur 30 min or longer after the administration of contrast agent. Another restriction is the lack of a standardized regimen for second-generation ultrasound contrast agents in children.

Nonetheless, we hope that our work, despite its limitations, will encourage further standardized, multicenter studies that will help determine the safety profile and value of ultrasound contrast agents for intravenous use in diagnostic imaging.

Acknowledgments—The study was financed by a National Science Centre grant on the basis of Decision No. DEC-2012/05/B/NZ5/01554. The authors do not report any financial or personal links with other persons or organizations that might negatively affect the content of this publication and claim authorship rights to this publication.

REFERENCES

- Bonini G, Pezzotta G, Morzenti C, Agazzi R, Nani R. Contrast-enhanced ultrasound with SonoVue in the evaluation of post-operative complications in pediatric liver transplant recipients. *J Ultrasound* 2007;10:99–106.
- Claudon M, Dietrich CF, Choi BI, Cosgrove DO, Kudo M, Nolsoe CP, Piscaglia F, Wilson SR, Barr RG, Chammas MC, Chaubal NG, Chen MH, Clevert DA, Correas JM, Ding H, Forsberg F, Fowlkes JB, Gibson RN, Goldberg BB, Lassau N, Leen EL, Mattrey RF, Moriyasu F, Solbiati L, Weskott HP, Xu HX. Guidelines and good clinical practice recommendations for contrast enhanced ultrasound (CEUS) in the liver— Update 2012: A WFUMB–EF-SUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. *Ultrasound Med Biol* 2013;39:187–210.
- Coleman JL, Navid F, Furman WL, McCarville MB. Safety of ultrasound contrast agents in the pediatric oncologic population: A single-institution experience. *AJR Am J Roentgenol* 2014;202:966–970.
- Cosgrove D. Ultrasound contrast agents: An overview. *Eur J Radiol* 2006;60:324–330.
- Darge K, Papadopoulos F, Ntoulia A, Bulas DI, Coley BD, Fordham LA, Paltiel HJ, McCarville B, Volberg FM, Cosgrove DO, Goldberg BB, Wilson SR, Feinstein SB. Safety of contrast-enhanced ultrasound in children for non-cardiac applications: A review by the Society for Pediatric Radiology (SPR) and the International Contrast Ultrasound Society (ICUS). *Pediatr Radiol* 2013;43:1063–1073.
- Greis C. Technology overview: SonoVue (Bracco, Milan). *Eur Radiol* 2004;8:11–15.
- Jacob J, Deganello A, Sellars ME, Hadzic N, Sidhu PS. Contrast enhanced ultrasound (CEUS) characterization of grey-scale sonographic indeterminate focal liver lesions in pediatric practice. *Ultraschall Med* 2013;34:529–540.
- Levano JA, Jimenez MA, Laiseca A, Vives R. Anaphylactic shock due to SonoVue. *Ann Allergy Asthma Immunol* 2012;108:208–209.
- McCarville MB, Kaste SC, Hoffer FA, Khan RB, Walton RC, Alpert BS, Furman WL, Li C, Xiong X. Contrast-enhanced sonography of malignant pediatric abdominal and pelvic solid tumors: Preliminary safety and feasibility data. *Pediatr Radiol* 2012;42:824–833.
- McMahon CJ, Ayres NA, Bezold LI, Lewin MB, Alonzo M, Altman CA, Kovalchin JP, Eidem BW, Pignatelli RH. Safety and efficacy of intravenous contrast imaging in pediatric echocardiography. *Pediatr Cardiol* 2005;26:413–417.
- Morel DR, Schwiager I, Hohn L, Terretaz J, Llull JB, Cornioley YA, Schneider M. Human pharmacokinetics and safety evaluation of SonoVue, a new contrast agent for ultrasound imaging. *Invest Radiol* 2000;35:80–85.
- Piscaglia F, Bolondi L. The safety of Sonovue in abdominal applications: Retrospective analysis of 23188 investigations. *Ultrasound Med Biol* 2006;32:1369–1375.
- Piskunowicz M, Kosiak W, Batko T. Intravenous application of second-generation ultrasound contrast agents in children: A review of the literature. *Ultraschall Med* 2012;33:135–140.
- Riccabona M. Application of a second-generation US contrast agent in infants and children—a European questionnaire-based survey. *Pediatr Radiol* 2012;42:1471–1480.
- Szebeni J. Complement activation-related pseudoallergy: A new class of drug-induced acute immune toxicity. *Toxicology* 2005;216:106–121.
- Valentino M, Serra C, Pavlica P, Labate AM, Lima M, Baroncini S, Barozzi L. Blunt abdominal trauma: Diagnostic performance of contrast-enhanced US in Children—Initial experience. *Radiology* 2008;246:903–909.