

Safety of Perfluorobutane (Sonazoid) in Characterizing Focal Liver Lesions

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Abstract

Background: The purpose of this study was to report the safety of perfluorobutane (Sonazoid) as a vascular-phase imaging agent in characterizing focal liver lesions (FLLs). **Materials and Methods:** From May 2014 to April 2015, a total of 54 individuals who received Sonazoid contrast-enhanced ultrasound (CEUS) were enrolled at 5 hospitals of 4 medical centers. All individuals were included in safety evaluation. A prospective study to evaluate the adverse effect (AE) incidences after intravenous administration of Sonazoid. **Results:** Sonazoid was well tolerated. Treatment-emergent adverse events (TEAEs) representing AE were recorded for 13 (24.1%) patients. The most common AE was abdominal pain (9.3%), followed by heart rate irregularity (5.6%). The majority of these patients (69.2%) experienced TEAEs that were mild in intensity. Sonazoid causes no significant AEs after intravenous injection. The only noteworthy AEs are related to tolerable myalgia (3.7%), abdominal pain (1.9%), and headache (1.9%). None of the 54 patients showed serious adverse effects. **Conclusion:** Sonazoid shows good safety and tolerance of intravenous use during CEUS of the liver for evaluation of FLLs.

Keywords: Contrast agent, focal liver lesions, microbubble, perfluorobutane, safety, Sonazoid, ultrasound

INTRODUCTION

Contrast-enhanced ultrasound (CEUS) by utilizing second-generation ultrasonic contrast agents (USCAs) has improved the assessment of liver parenchyma relative to the use of conventional ultrasound (US) (including gray-scale and color Doppler US) and exhibits high accuracy for differentiating malignant focal liver lesions (FLLs) from benign lesions.^[1] Sonazoid® (perfluorobutane microbubbles, GE Healthcare, Oslo, Norway), a new USCA with its hepatic parenchyma-specific Kupffer phase at CEUS, is very useful for detection and characterization of FLLs^[2-4] and now available in Japan, South Korea, Norway, and Taiwan (as of October 2018). The commercially available Sonazoid powder for injection consists of microspheres of perfluorobutane stabilized by a monomolecular membrane of hydrogenated egg phosphatidylserine, embedded in an amorphous sucrose structure.^[5] All the components are

not toxic to human body. However, deaths in critically ill patients who had undergone contrast echocardiography examinations had been reported even with no evidence of a causal relationship,^[6] therefore, the safety issue of Sonazoid has to be addressed.

The purpose of this study was to report safety of Sonazoid as a vascular-phase imaging agent in characterizing FLLs on the bases of a Phase III study conducted in Taiwan.

MATERIALS AND METHODS

A phase 3 prospective study was approved by an Independent Ethics Committee or Institutional/Independent Review Board according to national regulations with informed consent.

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Patient population

The patients enrolled must have had at least 1 untreated FLL but ≤ 8 lesions (excluding cysts) of <10 cm in diameter. The target FLL was selected at the discretion of the investigator. Female patients were not pregnant and nonlactating.

Exclusion criteria were ongoing chemotherapy or radiation therapy; allergies to eggs or egg products (hydrogenated egg phosphatidylserine sodium in Sonazoid may cause allergic symptoms);^[5,7] hypersensitivity to other component of Sonazoid; administration or scheduled administration of another contrast agent within 24 h before or after study participation; and thrombosis within the liver, portal, or mesenteric veins. Patients with the following conditions were also excluded: recent acute coronary syndrome or clinically unstable ischemic cardiac disease, adult respiratory distress syndrome, severe emphysema, pulmonary vasculitis, or history of pulmonary emboli, known right-to-left shunt, severe pulmonary hypertension, or uncontrolled systemic hypertension.

Ultrasound contrast agent

All patients received a single intravenous dose of Sonazoid (0.12 μ L/kg of perflubutane microbubbles). Sonazoid was reconstituted in accordance to the manufacturer's instructions.^[7] The injection of Sonazoid was followed by a flush with 5–10 mL of 0.9% sodium chloride.

Ultrasound equipments and contrast-enhanced ultrasound examination techniques

All US scanners used in the study (GE LOGIQ™ E9, Milwaukee, WI, USA; Philips iU22™, Bothell, WA, USA; and Toshiba Aplio™ 500, Tokyo, Japan) were equipped with low-frequency curved-array transducers (C6-1, C5-1, C2-6, respectively) for abdominal examinations. US settings (mechanical index [MI], frequency, frame rate, focal zone, depth, and gain) for the pre- and post-contrast liver examinations were adjusted to optimize the image quality for each patient, based on the different acoustic properties of Sonazoid.^[8] Digital video files and still images were recorded in the Digital Imaging and Communications in Medicine format. All patients received pre- and post-contrast imaging studies up to 10 min postinjection. All studies were recorded for reviewing.

Safety evaluation

Safety variables were assessed by on-site investigators or staff who were blinded to study contrast agents at baseline before contrast injection, at approximately 4-h postinjection, and at 24 h and 72 h via phone call. The severity of adverse events (AEs) were classified as mild, moderate, severe, and lethal based on the following grading criteria. Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated. Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Grade 3: Severe; medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Grade 4: Life-threatening;

urgent intervention indicated. Grade 5: Death related to an AE.^[9] All treatment-emergent adverse events (TEAEs) representing AE, and after injection changes in vital signs, clinical laboratory variables, physical examination status, and injection site monitoring were recorded and assessed.

RESULTS

From May 2014 to April 2015, a total of 54 individuals who received Sonazoid CEUS were enrolled at 5 hospitals of 4 medical centers in Taiwan. All individuals were included in safety evaluation.

Safety results

Sonazoid was well tolerated. Treatment-emergent AEs (TEAEs) were recorded for 13 (24.1%) of patients [Table 1]. The majority of these patients (69.2%) experienced TEAEs that were mild in intensity [Table 1]. The most common AE was abdominal pain, occurring in approximately 9.3% of patients, followed by heart rate irregularity (5.6%). That was related to ventricular premature contraction (VPC). Other TEAEs were myalgia (3.7%), headache, anemia, and pancytopenia (one each). Except for one patient with severe abdominal pain which lasted for 15 min, all others were transient and tolerable without medical intervention. Patients with anemia or pancytopenia (hemoglobin or cell counts showed 15% lower than that before CEUS) were asymptomatic and the decreased red blood cell and/or white cell counts were returned to normal within one week. None was associated with nausea, vomiting, fatigue, flushing, paresthesia, taste perversion, pruritus, rash, abnormal vision, dry mouth, dizziness, personality disorder, insomnia, nervousness, or hypoglycemia [Tables 2 and 3]. Although labile blood pressure

Table 1: Summary of treatment emergent adverse events by system organ class and preferred term (n=54)

System organ class preferred term	Individuals with a TEAE, n (%)	Even noted
Any TEAE	13 (24.1)	
Blood and lymphatic system disorders	1 (1.9)	4 hrs
Anemia	1 (1.9)	
Pancytopenia	1 (1.9)	
Endocrine disorders	0	
Hypoglycemia	0	
Gastrointestinal disorders	5 (9.3)	<24 hrs
Abdominal discomfort	1 (1.9)	
Abdominal pain	5 (9.3)	
Vomiting	0	
General disorders and administration site conditions	0	
Fatigue	0	
Pyrexia	0	
Vascular and other investigations	3 (5.6)	< 4 hrs
Blood in urine present	0	
Heart rate irregular	3 (5.6)	

TEAE: Treatment emergent adverse event, N: Total number of subjects exposed to Sonazoid, n: Number of individuals with TEAEs, Percentage: $n/N \times 100$

Table 2: Summary of treatment emergent adverse events by system organ class and preferred term (n=54)

System organ class and preferred term	Individuals with a TEAE, n (%)	Event noted
Musculoskeletal and connective tissue disorders	2 (3.7)	<24 hrs
Myalgia	2 (3.7)	
Nervous system disorders	1 (1.9)	<24 hrs
Headache	1 (1.9)	
Psychiatric disorders	0	
Anxiety	0	
Respiratory, thoracic, and mediastinal disorders	0	
Productive cough	0	
Skin and subcutaneous tissue disorders	0	
Rash	0	
Vascular disorders	6 (11.1)	<4 hrs
Labile blood pressure	6 (11.1)	

TEAE: Treatment emergent adverse event, N: Total number of individuals exposed to Sonazoid, n: Number of individuals with TEAEs, percentage: $n/N \times 100$

Table 3: Summary of moderate and severe intensity treatment emergent adverse events by system organ class and preferred term (n=54)

Preferred term intensity	Individuals with a TEAE, (n=54), n (%)
Any TEAE	
Moderate	1 (1.9)
Severe	1 (1.9)
Abdominal pain	
Moderate	1 (1.9)
Severe	1 (1.9)
Vomiting	
Moderate	0
Severe	0
Pyrexia	
Moderate	0
Severe	0

TEAE: Treatment emergent adverse event, N: Total number of individuals exposed to investigational medicinal product, n: Number of individuals with TEAEs, Percentage: $n/N \times 100$. A subject who experienced more than 1 occurrence of a TEAE was counted once for that TEAE, at the most severe intensity. A subject with multiple TEAEs within the same System Organ Class was counted once for that System Organ Class

(referred to as blood pressure change 15 % higher or lower than that before CEUS) was a relatively encounter (11%), it is a common situation noted in patients visiting a hospital.

Four patients (7.4%) experienced TEAEs for which there was a reasonable possibility that the contrast agent caused the event [Table 4]. However, all TEAEs were in grade 1 and classified as mild.

DISCUSSION

The second-generation microbubble USCA, such as SonoVue (Bracco, Milan, Italy) and Sonazoid (GE Healthcare,

Waukesha, WI, USA), have considerably improved the diagnostic yield of US imaging for the evaluation of focal hepatic lesions in recent years because of its ability to depict tumoral vascularity at CEUS study. In addition, CEUS has the advantage of the absence of ionizing radiation, the widespread availability, even at the bedside, and the possibility to characterize a lesion when detected on conventional US which is commonly used as the first imaging modality for exploration of the liver.

Sonazoid-reconstituted product contains approximately 8 μ L microspheres/mL with median diameter of approximately 2.6 μ m. Sonazoid after reconstitution is a suspension of microbubbles. Each of the bubbles is coated by a monomolecular membranous shell of hydrogenated egg phosphatidylserine that prevents diffusion of encapsulated perfluorobutane gas. The product contains approximately 1.2 billion microspheres/mL, of which <0.1% are larger than 7 microm. The microsphere size perfectly fit the microcirculation of the systemic and pulmonary vascular beds without the risk of embolism. The stability of Sonazoid after reconstitution is good, with no significant changes in physicochemical properties 2 h after reconstitution. Pressure stress is well tolerated by both concentrated and diluted Sonazoid with no permanent effects of pressures up to 300 mmHg. The level and consistency of the investigated physicochemical properties demonstrate that Sonazoid should be well suited as a contrast agent for medical imaging with medical US.^[5]

When USCA are introduced in the body, they increase the acoustic scattering from the tissues through which they pass, and especially from the vasculature. Their primary uses lie in cardiological and oncological imaging. However, these microbubbles have the potential to act as centers for acoustic cavitation activity, and so, it is important to consider the safety of their use from an acoustic standpoint.^[10] When exposed to US field, the USCA microbubbles undergo volumetric oscillation. The use of USCA for diagnostic US induces biological effects caused by both thermal and mechanical mechanisms; however, the mechanical effect is dominant. Since the sound wave is a kind of mechanical pressure wave with condensation (positive pressure) and rarefaction (negative pressure) components, a volumetric change during bubble expansion under negative US pressure is larger than that during bubble contraction under positive US pressure, and the volumetric changes depend not only on the peak pressure but also on the duration of the pressure. Therefore, the MI defined by the following equation is also a convenient index used for estimation of the extent of bubble oscillation.

$$MI = \frac{P_r}{\sqrt{f}},$$

Where P_r is peak negative pressure of a diagnostic US pulse and f is the center frequency of US in MHz.

With high power and high MI, the microbubble might be destructed and the cell may be injured.

Table 4: Summary of Treatment emergent adverse event related to treatment by system organ class and preferred term (n=54)

Preferred term	Individuals with a TEAE, (n=54), n (%)
Any TEAE	4 (7.4)
Abdominal pain	1 (1.9)
Headache	1 (1.9)
Myalgia	2 (3.7)

TEAE: Treatment emergent adverse event, N: Total number of individuals exposed to Sonazoid, n: Number of individuals with TEAEs, Percentage: $n/N \times 100$

The present study aims at reporting our prospective safety evaluation data and presenting a balanced account of the existing articles regarding the mechanisms and clinical implications of echo-contrast bioeffects, to make an informed assessment of their safety in clinical practice at assessment of patients with FLLs. Our results, although with relatively small number of patients, also confirm other studies with higher number of patients and reviews, showing good safety and tolerance of intravenous administration of Sonazoid during CEUS of the liver for evaluation of FLLs. In one of the most important prospective studies on Sonazoid by Moriyasu and Itoh, the incidences of AEs were as high as 49.2%.^[2] Although it is much lower (24.1%) in our study, the incidence is still considered high. That is probably due to the strict definition of the AEs. Actually, 3 patients in our series with abdominal pain had a history of irregular bowel movements or irritable bowel syndrome, and one patient with headache had a history of tension headache off and on. Moriyasu and Itoh attributed that the AEs could be caused by the primary diseases or underlying cancer itself.^[2] The majority of AEs were mild in intensity and self-limited. In Moriyasu and Itoh's series, none was considered peculiar to perfluborbutane microbubbles. A limitation to this study was small number of patients even though it suggested that Sonazoid is a safe contrast agent.

While there is no proven clinical evidence of harm or adverse effects on the human liver resulting from clinical use of these agents, caution is recommended when contrast-enhanced imaging is undertaken, although a theoretical possibility exists that the interaction of diagnostic US and microbubble USCA could produce certain bioeffects.^[11] Cellular effects that have been observed *in vitro* include sonoporation, hemolysis, and cell death.^[12] Data from small animal models suggest that microvascular disruption can occur when microbubbles are insonated.^[13,14] Thus, in general, low MI should be preferred for CEUS of the liver. Some specialized imaging methods have been developed to preferentially detect echoes from the contrast bubbles while reducing those from other structures, such as solid tissue. This resulted in a better detection and display of the microcirculation using USCA and new imaging strategies, mainly nonlinear techniques.^[15-18]

Reduction of contrast agent dose, reduction of the duration of examination, and imaging with higher US frequency may

further reduce the likelihood of bioeffects.^[19] If diagnostic information can only be obtained using high MI sequences, the benefits versus the risks of the procedure should be assessed and the mode should be carefully selected for the benefit of the patient.^[20,21] Since there may still be unknown effects at interaction of US and microbubble contrast agent, it is recommended by the WFUMB Safety Committee that the principle of "as low as reasonably achievable" should be followed.^[19]

CONCLUSION

Perfluborbutane (Sonazoid) causes no significant AEs after intravenous injection, and shows good safety and tolerance in patients with focal liver lesion(s) during and after intravenous administration for CEUS

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Conflicts of interest

There are no conflicts of interest.

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