Eur. Radiol. 9 (Suppl. 3), S 347–S 348 (1999)

European Radiology

SonoVue, a new ultrasound contrast agent

M. Schneider

Bracco Research SA, 31, route de la Galaise, CH-1228 Plan-les-Ouates Genève, Switzerland

Introduction

SonoVue is the trademark of a new ultrasound contrast agent formerly known as BR1 [1]. SonoVue is a suspension of stabilized sulfur hexafluoride (SF_6) microbubbles with remarkable properties. The bubble suspension is easily reconstituted from a lyophilisate by addition of saline. The high bubble concentration (up to 5×10^8 bubbles/ml), combined with a favorable size distribution profile, provides strong echogenicity over the entire medical frequency range (1–10 MHz). With a mean diameter of 2.5 μm and more than 90% of the bubbles smaller than 8 μm, the microbubbles in SonoVue are small enough to avoid trapping in the capillary vasculature. Reconstitution of bubbles is complete without the need for complex bubble activation or the potential hazard of in vivo bubble production. After reconstitution, the suspension is stable for hours and even days at room temperature. Because the product contains no preservatives, the maximum use time for the reconstituted SonoVue is limited to 4 h. The use of SF_6, a totally innocuous and inert gas, rather than air, provides the bubbles with a high resistance to pressure increases such as the ones which occur in the left heart ventricle during systole, or during passage through the lung capillary bed or through the coronary circulation. As a consequence, SonoVue shows excellent bubble survival allowing for left ventricule and other organ visualization.

Safety studies

Pre-clinical studies in a variety of animal models have shown SonoVue to be physiologically inert and to produce homogeneous left-heart opacification at dosages of 0.03 ml/kg or less. At the same dosages, SonoVue produces an increase in intensity of spectral, color, and Power Doppler signals in peripheral vessels. Chronic toxicological studies were performed with SonoVue at doses up to 5 ml/kg administered intravenously in rats and monkeys, and no specific adverse event or safety issues were observed or identified. In fact, there was no difference between SonoVue and saline with regard to safety. In our experience the total quantity of gas administered and the control of the size of the bubbles are key parameters for the safety of ultrasound contrast agents. The potential risk of gas embolism associated with SonoVue was investigated in the rat (unpublished data). SonoVue was administered directly into the carotid artery of the rat at a dose of 1 ml/kg corresponding approximately to 30 times the expected human dose. The possible presence of cerebral ischemic lesions was assessed after histological staining of the brain tissue and by assaying the neuron-specific enolase (a specific marker of neuronal damaging) in the cerebrospinal fluid. No ischemic effects were observed after SonoVue administration, whereas clear ischemic effects were noticed after injection of as little as 10^5 polystyrene microspheres of 15-μm size [2].

SF_6 is a very safe gas already approved for the treatment of retinal detachment by pneumatic retinopexy [3]. Due to the very small total bubble volume in SonoVue (approximately 5 μl/ml), the quantity of gas bubbles administered remains extremely low even at the highest doses, typically less than 20 μl per subject.

Pharmacokinetics

After intravenous injection, SonoVue microbubbles persist in the blood stream much longer than air bubbles of similar size. This is due to the low solubility of SF_6 in water and to a slow diffusion from the bubbles to blood. The microbubbles remain in the intravascular space and are capable of traversing the pulmonary and systemic capillary network. Of particular importance SonoVue is not trapped in the microcirculation nor is there diffusion across vascular or microvessel walls.

A pharmacokinetic study of SonoVue has been carried out on the component SF_6 after a single intravenous injection of SonoVue at 0.3 and 1 ml/kg in the rabbit. SF_6 was exclusively eliminated via the lungs. More than

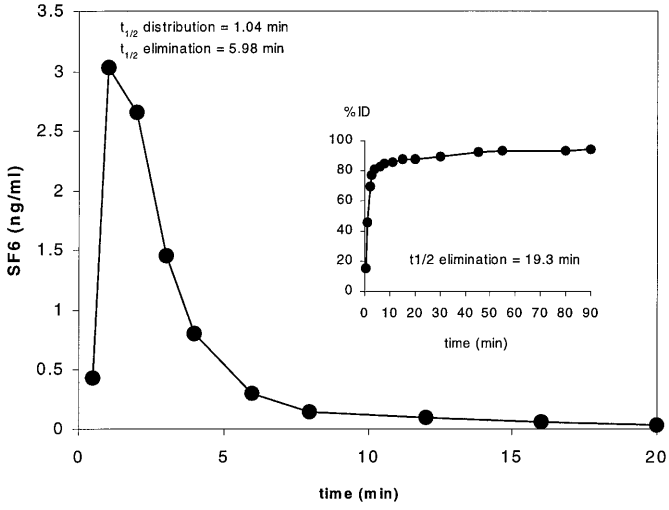

Fig. 1. SF_6 blood level after intravenous administration of SonoVue (0.3 ml/kg) in man. *Inset:* cumulative pulmonary excretion of SF_6

90% of the injected SF_6 was excreted in expired air within a few minutes after administration. The elimination of SF_6 from blood was also extremely rapid (Fig. 1). Because of this outstanding safety profile and the pharmacokinetics, single or multiple administrations of SonoVue are possible without any accumulation of contrast agent in blood.

Clinical studies

The development of SonoVue is focusing on two major areas, cardiology applications and radiology. Left ventricle opacification was observed in B-mode echocardiography at doses as low as 0.003 ml/kg [4]. The duration of left-ventricle contrast enhancement was dose related, lasting 7–8 min after a SonoVue dose of 2 ml per subject.

Doppler investigations of renal arteries, portal vein, and middle cerebral arteries showed strong enhancement of the Doppler signal following intravenous injections of 0.15–4.8 ml per subject [5]. At 1.2 ml, approximately 7 min of definite and clinically useful enhancement was observed with continued contrast enhancement lasting up to 10–12 min.

References

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