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Pharma Middle East 2015: Therapeutic micro-bubbles for diagnostic and drug delivery modalities

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Abstract

Cancer treatment usually involves systemic injection of toxic chemotherapeutic agents that cause severe side effects for the patient; it is also relatively inefficient use of expensive toxic drugs. The area of targeted drug delivery in which drugs are delivered in a carrier directly to the cancer has gained much interest in recent years. This approach reduces the side effects of the drug and also provides a direct localized, high-concentration treatment. Micro-bubbles (MBs) as used for Contrast Enhanced Ultra Sound (CEUS) imaging are micron sized gas encapsulated spheres, stabilized with a shell of biocompatible material (e.g., proteins, phospholipids). These MBs are capable of circulating in the vasculature; their high acoustic impedance mismatch with the surrounding tissue provides a strong enhancement of the ultrasound imaging. Two possible strategies for delivering drugs and genes with microbubbles are emerging. The first consists on the ultrasound-mediated microbubble destruction, which is based on the cavitation of microbubbles induced by ultrasound application, and the second is the direct delivery of substances bound to microbubbles in the absence of ultrasound. Different drugs and genes can be incorporated into the ultrasound contrast agents. It has already been demonstrated that perfluorocarbon-filled albumin microbubbles avidly bind proteins and synthetic oligonucleotides. In a similar way, microbubbles can directly take up genetic material, such as plasmids and adenovirus, and phospholipid-coated microbubbles have a high affinity for chemotherapeutic drugs. Furthermore, specific ligands for endothelial cell adhesion molecules, such as P-selectin and leukocyte intercellular adhesion molecule 1 (ICAM-1), can be attached to both lipid- and albumin-encapsulated microbubbles, which increases their deposition to activated endothelium.

The mechanisms by which ultrasound facilitates the delivery of drugs and genes result from a complex interplay among the therapeutic agent, the microbubble characteristics, the target tissue, and the nature of ultrasound energy. The presence of microbubbles in the insonified field reduces the peak negative pressure needed to enhance drug delivery with ultrasound. This occurs because the microbubbles act as nuclei for cavitation, decreasing the threshold of ultrasound energy necessary to cause this phenomenon. The results of optical and acoustical studies have suggested the following mechanisms for microbubble destruction by ultrasound: 1- gradual diffusion of gas at low acoustic power, 2- formation of a shell defect with diffusion of gas, 3- immediate expulsion of the microbubble shell at high acoustic power, and 4- dispersion of the microbubble into several smaller bubbles. Cavitation of the bubbles is characterized by rapid destruction of contrast agents due to a hydrodynamic instability excited during large amplitude oscillations, and is directly dependent on the transmission pressure. It has been reported that the application of ultrasound to contrast agents creates extravasation points in skeletal muscle capillaries, and this phenomenon is dependent on the applied ultrasound power. High intensity ultrasound (referred to as a high mechanical index) can rupture capillary vessels, resulting in deposit of protein and genetic material into the tissues. Skyba et al demonstrated in an exteriorized spinotrapezius preparation that ultrasonic destruction of gas-filled microbubbles caused rupture of microvessels with diameter ≤ 7 μm (capillaries), with local extravasation of red blood cells. Price et al have shown that polymer microspheres could be driven as much as 200 μm into the parenchyma with this method. The authors calculated that only a small number of capillary ruptures were required to deliver large quantities of the colloidal particles to the muscle. Using the same model of polymer microspheres bound to microbubbles and ultrasound, it has also been demonstrated that the ultrasound pulse interval and microvascular pressure influence the creation of extravasation points and the transport of microspheres to the tissue. Both were greatest when the pulse interval was around 5 seconds, which allows maximal microbubble replenishment within the microcirculation after destruction by the ultrasound pulse.

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The formation of pores in the membranes of cells as a result of ultrasound-induced microbubble cavitation has been proposed as a mechanism for facilitating the drug deposition. Taniyama et al demonstrated the presence of small holes in the surface of endothelial and vascular smooth muscle cells immediately after transfection of a plasmid DNA by ultrasound-mediated microbubble destruction, using electron microscopic scanning. It was then postulated that these transient holes in the cell surface caused by microbubbles and ultrasound resulted in a rapid translocation of plasmid DNA from outside to cytoplasm. Mukherjee et al demonstrated by electron microscopy of a rat heart performed during application of ultrasound, that disruption or pore formation of the membrane of the endothelial cells occurred with acoustic power of 0.8 to 1.0 W/cm2. However, it was a lower intensity of ultrasound (0.6 W/cm2) that caused more drug delivery with microbubbles. More recently, voltage clamp techniques were used to obtain real-time measurements of membrane sonoporation in the presence of albumin-coated microbubbles (Optison). Ultrasound increased the transmembrane current as a direct result of membrane resistance due to pore formation.

Another important therapeutic property of microbubbles is their increased adherence to damaged vascular endothelium. Albumin-coated microbubbles do not adhere to normally functioning endothelium, but their adherence does occur to activated endothelial cells or to extra-cellular matrix of the disrupted vascular wall, and this interaction could be a marker of endothelial integrity Because of this characteristic, the delivery of drugs or genes bound to albumin-coated microbubbles could be selectively concentrated at the site of vascular injury in the presence or absence of ultrasound application.

More recently, there has been considerable interest in the development of MBs as vehicles for drug delivery, by loading them with liposomes encapsulating a drug, the whole complex is functionalized and targeted toward the required location using antibodies, or other ligands. Here I am presenting our group at the University of Leeds (Leeds, UK) developing therapeutic micro-bubbles that act as both agents for CEUS imaging and targeted drug-delivery vehicles. Ultimately, a large amplitude sound wave is used to destroy the bubbles and trigger release of the drug at the targeted tumor. Theranostic MBs are a simple and versatile drug-delivery technique that could potentially improve cancer treatment, both in terms of patient experience and overall drug efficiency. Importantly, they offer new ways of delivering hydrophobic drugs, which have traditionally been difficult to deliver efficiently.

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