Effects of Administration Routes on MicroCT Imaging Characteristics of a Long-Acting Vascular Contrast Agent in a Murine Model

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Introduction

High-resolution microCT systems capable of sub 20-micron isotropic spacial resolution provide an attractive new approach for noninvasively studying models of human diseases in live small animals.[1,2] However, relatively long acquisition times preclude the use of conventional water-soluble contrast media for imaging pathological conditions associated with vascular abnormalities. Utilizing the ability of PEG chains to modify surfaces of biological macromolecules, we have developed a long-acting blood-pool contrast agent (BP) based on our hepatocyte-selective CT contrast agent platform for vascular microCT imaging applications.[3,4] Macromolecular structures of BP and ITG particles are shown in Fig 1. Incorporation of PEG moieties into the phospholipid monolayer shell of the ITG vehicle interferes with the association of Apo-E, which is believed to be essential for hepatocyte recognition. Delaying the sequestration of ITG by liver cells results in prolonged vascular residence time. The vascular contrast agent is now known as Fenestra™ VC.

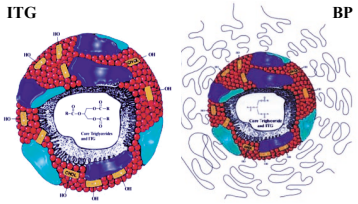


Fig 1. Structure of BP and ITG Particles

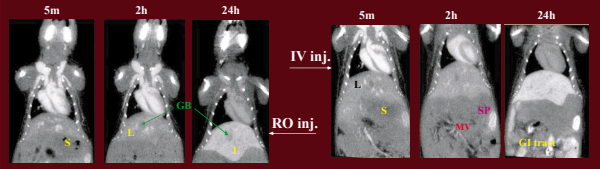
Fenestra VC is typically administered to mice through the tail vein. However, being highly proficient at giving tail vein injections can be quite challenging. To alleviate this matter, we set out to evaluate the in vivo imaging efficacy of this long-acting vascular contrast agent following administrations through retro-orbital (RO) sinus and intraperitoneal (IP) space as alternative injection routes .

Materials and Methods

The blood-pool contrast agent (Fenestra VC) was obtained from ART Advanced Research Technologies (Montreal, Canada). The finale iodine concentration and mean particle size of this lipid emulsion were 50 mg I/mL and 180 nm, respectively. Mice were placed on soft diet at least 1 day prior to the initiation of the study for minimizing streak artifacts produced by rodent chow. Anesthetized female C57Bl/6 mice (2-3 per group) were given a single 15 mL/kg dose of the BP via three different routes (i.v., i.p. and retro-orbital injections. The mice were scanned using a GE eXplore Locus microCT system (80 kVp, 450 µA, 200 msec/view, 5 frames/view, 400 views/scan and 93 µm3 resolution) prior to and at predetermined time intervals following administration .

Images were reconstructed with the EVSBeam software (GE Medical System) and subsequently displayed and analyzed using both Amira 3-D visualization software (V3.1) and MicroView program. CT values of volumetric ROIs in the inferior vena cava (IVC) and liver were normalized to Hounsfield Units (HU). Normalized signal intensity (HU/voxel) was obtained from the difference of enhanced SI and the baseline value.

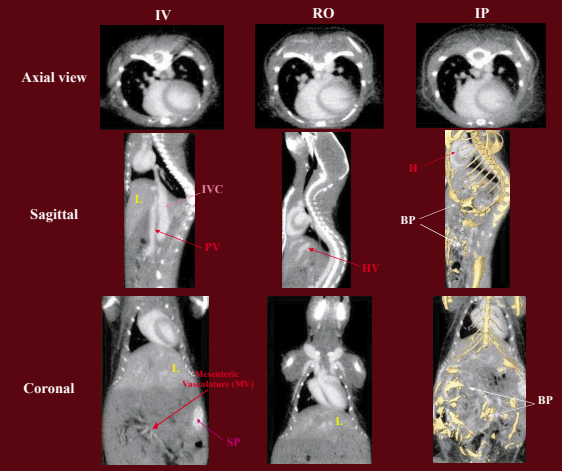
Fig 2. VC-enhanced microCT vascular images of C57Bl/6 mice following RO or IV injections of Fenestra VC (15 mL/kg) at various timepoints.



Following an RO injection, the blood-pool agent diffuses into the circulation over a period of 20-30 minutes, producing excellent vascular contrast enhancement (Fig 2.). Coronal images of female mice acquired 5 minutes after RO and IV injections of Fenestra VC depicted a comparable level of vascular contrast intensitywas achieved. Hepatobiliary elimination of the agent is evident after 24 hours as indicated by increased intensity in the gall bladder, liver, and intestines.

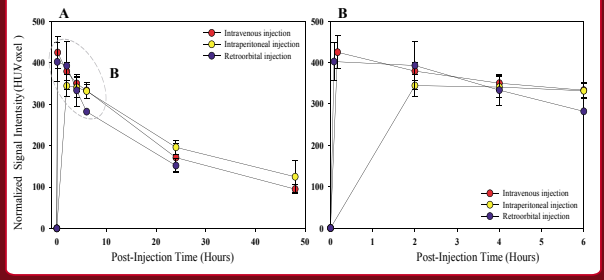
Results and Discussion

Fig 3. VC-enhanced microCT vascular images of C57Bl/6 mice 2 hours following a single injection of Fenestra VC (15 mL/kg) via various routes.



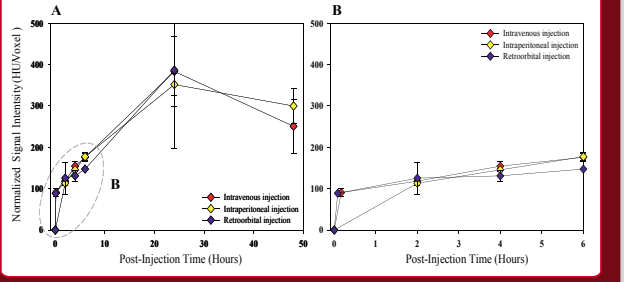
Axial, coronal and sagittal images of C57Bl/6 mice obtained 2 hours after administration of Fenestra VC (15 mL/kg) via IV, IP, and RO routes are shown in Fig 3. The images clearly demonstrated the blood-pool agent continues to produce excellent vascular contrast enhancement 2 hours after injections via IV and RO routes. For the IP route, vascular signal intensity became peaked after 2 hours, although a relatively small portion of the injected dose was still visible in the intraperitoneal space. This administration route is not desirable for identifying blood vessels in the abdominal area owing to the present of the contrast agent in the intraperitoneal space.

Fig 4. Normalized time-signal intensity profiles of Fenestra VC (15 mL/kg) in the IVC following administrations via iv, ip and retro-orbital routes.



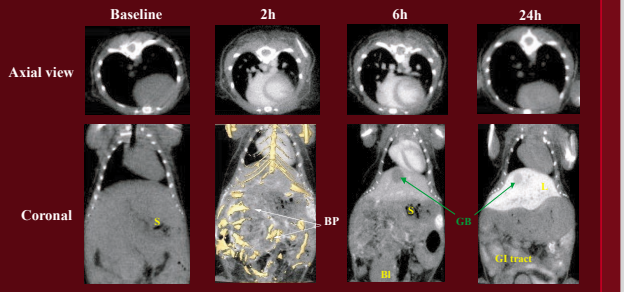
Effects of administration routes on the vascular kinetics profiles of Fenestra VC in female C57Bl/6 mice are shown in Fig 4. Vascular intensities obtained following an IV or RO injection were insignificantly different. A 2-hour delay in the time to achieve maximal vascular CT values was observed following IP administration (Fig 4B). Regardless which route the blood pool contrast agent was administered, more than 75% of the injected dose was retained in the blood stream after 6 hours, producing prolonged vascular enhancement contrast enhancement.

Fig 5. Normalized time-signal intensity profiles of Fenestra VC (15 mL/kg) in the liver following administrations via IV, IP, and RO injections.



Time-intensity profiles exhibited a rapid uptake of Fenestra VC by the liver cells, resulting in the removal of the majority of the blood-pool agent from the circulation after 24 hours following administration via all three routes (IV, IP and RO) as shown in Fig 5A. Liver intensities increased slightly after 3 hours as initial elimination of the contrast agent began.

Fig 6. VC-enhanced microCT vascular images of C57Bl/6 mice following an IP injection of Fenestra VC (15 mL/kg) .



Diffusion of Fenestra VC into the blood following an IP injection of 15 mL/kg dose in C57Bl/6 mice took 4-6 hours, indicated by the present of the agent in the intraperitoneal cavity (Fig 6). Excellent vascular contrast enhancement and soft tissue identification were observed at 6 hours post injection. Enhancement of the gall bladder and gastrointestinal tract was noticed after 24 hours, indicating fecal elimination of the agent.

Conclusions

Intravenous, intraperitoneal, and retroorbital injections of Fenestra VC produced a comparable level of vascular contrast enhancement. Therefore, any of these administration routes can be used which may be advantagous to investigators without technical expertise in tail vein injection.

References

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