8 Summary

Magnetic resonance imaging and histological studies on the behavior of a monomer stabilized superparamagnetic contrast medium for Magnetic Resonance Angiography in rat model

The aim of the present study was to investigate a new, monomer-coated superparamagnetic contrast medium for magnetic resonance angiography. This was done by magnetic resonance imaging (MRI) and histologic examinations performed to characterize the contrast medium VSOP-C63 in the rat model. A total of 101 rats were examined to determine the optimal dose and the blood half-life as well as the distribution and degradation of the contrast medium in connection with a histopathologic evaluation.

The MRI results obtained with a high-resolution 3D FLASH sequence showed a prolonged intravascular signal increase for all dosages (15, 30, 45, 60, 75 and 90 µmol/kg body mass (BM)) tested in 36 rats. The observed signal increase allowed for even delineating small, second- and third-order vessels. Blood half-lives were found to be dose-dependant. Significant differences in signal increase among the dosages tested were observed for doses up to 75 µmol/kg BM. The dose of 90 µmol/kg BM produced an overdose effect which was superimposed on the signal-enhancing effect at the early time points. With a time-optimized acquisition technique, bolus injection of VSOP-C63 at a dose of 45 µmol/kg produces the same signal-enhancing effect in the aorta as the injection of 0.2 mmol Gd/kg (Magnevist®). This is due to the favorable R2-to-R1 ratio of VSOP-C63, which is 1.3 as determined at 37°C in 0.9% NaCl using a field strength of 0.47 T.

MRI and histologic examinations in 65 rats, among them 30 control animals, revealed differences in iron accumulation from the contrast medium between the liver and the spleen. The signal intensities determined using a proton-density-weighted SE sequence and a T2-weighted GRE sequence at 1.5 Tesla suggest that VSOP-C63 accumulates mainly in the liver and to a lesser extent in the spleen. Maximal iron accumulation after administration of the contrast medium is complete after 24 hours, when metabolization of the particles starts. Metabolization is different in the liver and the spleen. While traces of iron from the contrast medium can still be found in the liver after two months of continuous metabolization, the iron

from the contrast medium completely disappears from the spleen within one week of contrast medium injection. At one and two months after contrast medium injection, renewed signal loss due to the beginning physiologic storage of the iron was observed. Iron determinations revealed no age dependence in the liver tissue of rats with a body mass of up to 500 g whereas the spleen showed a marked increase in the amount of physiologically stored iron with age. Examination of the control animals demonstrated that the signal intensities of the spleen changed with age. Animals with a body mass of 280 g or above, which corresponds to an age of about 55 days, showed large amounts of iron in the spleen. Animals below this limit displayed only slight to moderate physiologic iron storage. Since the body's intrinsic iron stores, if they are large enough, likewise produce a signal reduction, the animals' age must be taken into account when investigating superparamagnetic iron oxide particles. In contrast, age plays no role for liver imaging in the age group investigated in this study (up to a maximum of 500 g). The two MRI sequences used in this study showed similar characteristics in the liver and in the spleen with the more sensitive T2-weighted GRE sequence depicting a more pronounced signal loss. The precision of the proton-density-weighted SE sequence and the sensitivity of the T2-weighted GRE sequence together present a useful combination for determining the signal behavior of a contrast medium dose over time.

The histologic examinations of the control animals demonstrated physiologic iron in the lungs and kidneys but not in the liver and the heart. Following contrast medium injection, iron oxide particles were taken up by the cells of the mononuclear phagocytosing system. This uptake was most pronounced in the liver, where iron was predominantly taken up by peripherolobular Kupffer's cells. Only little contrast medium iron is taken up by the spleen but the signal loss produced is likewise pronounced due to the Spinell structure. The results suggest that in the course of metabolization of the contrast medium iron from the liver and spleen, there is an increase of iron storage in other organs, especially in the lungs and kidneys but to a lesser degree also in the heart. However, one must bear in mind that these organs also show physiologic iron storage with increasing age (Casale et al., 1981; Massie et al., 1983).

The morphometric results (number of particles, surface, and particle size) show a highly positive correlation with the signal intensities at MRI as long as the contrast medium iron particles preserve their Spinell structure. The surface of the iron particles in the contrast medium animals increases one and two months after injection without any effect on the other parameters. This observation may be attributed to a different mode of storage resulting from

redistribution of the iron. It may be speculated that individual particles within a cell fuse to form larger particles or a single large particle in the course of time.

The MRI data in combination with the macroscopic and histopathologic findings show that the new contrast medium VSOP-C63 is a well-tolerated agent that is unlikely to produce any adverse reactions at a dose of 60 μmol Fe/kg BM. With its extended equilibrium phase and excellent imaging properties, VSOP-C63 is a promising candidate for MR angiography and represents an alternative to the agents currently used in clinical routine.