Longitudinal Helium-3 and Proton imaging of magnetite biodistribution in a rat model of instilled nanoparticles

A. Al Faraj[1], G. Lacroix[2], H. Al Said[1], D. Elgrabi[2], V. Stupar[1], F. Robidel[2], S. Gaillard[1], E. Canet-Soulas[1], and Y. Crémillieux[1]

[1]Laboratoire de RMN, Université Lyon 1, Villeurbanne, France, [2]INERIS, Verneuil-en-Halatte, France

INTRODUCTION

Epidemiological and toxicological studies have provided evidence that ultrafine particles in the nanometric range can induce chronic or acute health damage when accidentally inhaled. MRI, as a non-invasive imaging technique, has the potential for assessing the biodistribution evolution of magnetically labelled nanoparticles and the lung functional alterations induced by the nanoparticles. In this study, we report the follow-up of USPIO (ultra-small iron oxides nanoparticles) distribution in lungs, liver, spleen and kidneys using Helium-3 and proton MRI in a rat model of intrapulmonary distributed nanoparticles.

METHODS

Twelve male Sprague-Dawley distributed in 3 groups were imaged. Seven animals were intra-tracheally instilled with a 0.15 ml suspension of 0.5 g of magnetite nanoparticles (20-30 nm diameter). Three control animals were instilled with 0.15 ml saline solution. A second control group (n=2) underwent an intravenous injection of 0.5 g of magnetite suspension. Helium-3 acquisitions were performed on a 2 Tesla magnet. Following anesthesia, a breathing mask was fitted on the rat head and the animal was allowed to breathe freely from a Helium-3 reservoir during ventilation image acquisition (20 seconds total acquisition time). Helium-3 ventilation images were acquired with two different echo time (40 μs and 1 ms). Proton imaging was then performed on a 4.7 T magnet using a gradient echo sequence (TR/TE= 380/5 ms; 30° flip angle; 2 mm slice thickness). Axial slices were positioned in order to image the liver, the spleen and the kidneys. Respiratory gating was used. The imaging protocol was repeated for each animal at day 0, 2, 7 and 14. After completion of the 2-weeks imaging protocol, the animals were sacrificed. The blood was collected and the following organs (lungs, liver, kidneys, spleen, heart, brain, thymus and testicles) were removed for iron dosage by ICP-OES (Inductively Coupled Plasma – Optical Emission Spectrometer) and histological analysis.

RESULTS

The Helium-3 images acquired with the short echo time demonstrated homogeneous ventilation of the lungs (Figure 1) and it was not possible based on this short echo time images to differentiate between control animals and those instilled with the magnetite suspension. For ventilation images acquired with longer echo times, hypo-intense and void signal regions were observed in all the animals instilled with the magnetite suspension (Figure 1). During the 2-weeks investigation study, the lung ventilation images gradually moved to a more homogeneous pattern with increasing signal intensity (Figure 1 and 2). The two control groups (saline instillation and magnetite suspension injection) did not exhibit any detectable signal intensity decrease. In the magnetite instilled animal group, the CNR (contrast to noise ratio) values in liver, spleen and kidneys measured on proton images stayed unchanged during the 2-weeks investigation and were not statistically different from the values obtained in control animals. For animals injected with magnetite suspension, it was observed as expected a 3 to 5 fold CNR increase in liver and spleen during the 2-weeks duration of the study. In the magnetite instilled group, the concentration of iron in the lungs measured at day 14 by ICP-OES was equal to 86% of the initial instilled iron concentration. Iron concentrations in the blood, liver, spleen, kidneys and thymus of instilled animals were not statistically different from control animals. The histological slices of the control and instilled rats did not show any pulmonary lesions. The presence of iron-filled alveolar macrophages was observed in the instilled group on the histological slices.

DISCUSSION AND CONCLUSIONS

The presence of magnetite in lungs during the 2-weeks investigation was observed using the Helium-3 ventilation image and was confirmed with ex-vivo iron dosage. The absence of increased iron concentration in organs other than lungs was demonstrated using either in-vitro analysis techniques or MRI. Both in-vivo MRI and post-mortem analysis demonstrated that the passage of the USPIOs from the alveolar space to the systemic circulation and their accumulations in organs other than lung is limited. Work in progress includes quantitative measurement of magnetite concentration based on the Helium-3 ventilation images. This study illustrates the potential of non-invasive Helium-3 and proton imaging protocols for assessing longitudinally the distribution of intrapulmonary magnetically labelled nanoparticles. In the future, this approach could prove useful for investigating the biodistribution, the clearance and the biological effects of inhaled or instilled nanoparticles.

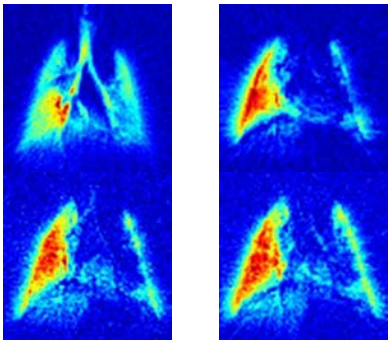

Figure 1. Ventilation images obtained in an animal instilled with magnetite suspension. Top left: short (40 μs) echo time image. Top right: 1-ms echo time acquired at day 2. Bottom left: 1-ms echo time acquired at day 7. Bottom right: 1-ms echo time acquired at D14.

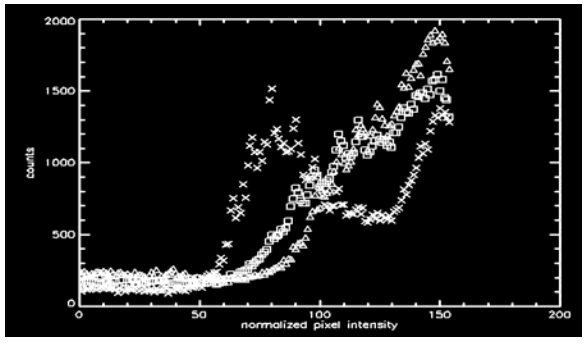

Figure 2. Pixel intensity histograms from ventilation images shown in Figure 1. Day 2 (X), 7 (□) and 14 (Δ).