Fluorinated Anaesthetics Uptake Kinetic Investigation on Large Animal Model using 19F MRS/MRI

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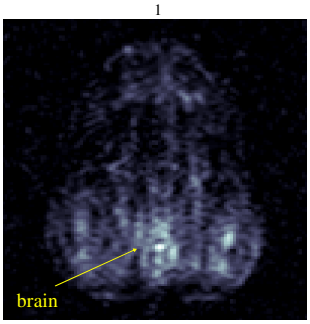
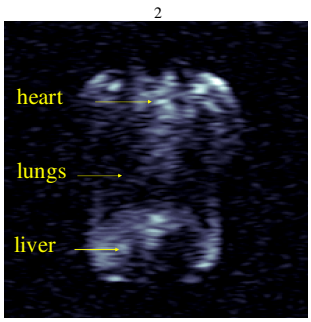
Introduction

Drug imaging is an emerging tool, which contributes to the development and understanding of pharmacons. Some drugs, e.g. the inhaled anesthetics isoflurane, sevoflurane and desflurane, embody fluorine. In these cases, ^{19}F MRI allows for in vivo imaging as the background signal of fluorine is negligible. Additionally, using NMR spectroscopy methods the chemical shift of fluorine-19 provides an insight into the molecular interactions as well as into the metabolism of these substances. Xu and coworkers investigated fluorinated anesthetics in a rat model using a 4.7 T scanner. They studied the sevofluran uptake, distribution and elimination in brain. With the help of T_2 relaxation analysis they were able to discriminate two compartments of sevofluran molecules with different mobility providing more details about the mechanisms of action of these anesthetics. Here, we established a large animal model for NMR/MRI investigations of fluorinated anesthetics at standard 1.5T medical scanners, which may yield additional pharmacological findings and may be considered as a further step towards potential human studies.

Materials and methods

With approval of the local animal care committee, uptake, distribution and elimination of fluorinated anesthetics were investigated in five domestic pigs (20-25 kg). After induction of anesthesia with propofol and fentanyl and endotracheal intubation the animals underwent ventilation in the volume controlled mode using a semi-closed breathing system (Sulla 808 V®; Draeger, Luebeck, Germany) with a fresh gas flow of 4 l/min. Inhaled anesthetics (servofluran and desfluran) were delivered by a vaporizer (Vapor, Draeger) at concentrations of 4-5% while the kinetic of the anesthetic uptake in brain was recorded by ^{19}F NMR spectroscopy (100mm-slice selective). In the same time, inspiratory and end expiratory anesthetic gas concentrations were registered by an anesthesia monitor (S/5, Datex-Ohmeda, Helsinki, Finland). When both concentrations values reached the saturation plateau (40 minutes after starting the inhaled anesthetics delivery), cranium and trunk were scanned by 19F MRI to map the concentration distribution. The measurements were performed on a 1.5T broadband MRI scanner (Vision, Siemens, Erlangen, Germany) equipped with a 19F birdcage coil of 25 cm diameter (Rapid Biomedical, Wuerzburg, Germany). A 2D FLASH sequence (TE/TR/FA=4ms/700ms/60°) without slice selection was applied in coronal projection. Setting the imaging matrix to 64x128 (at FOV=300mm) a total measurement time of 32 minutes was achieved.





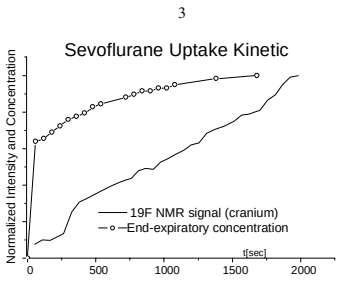


Fig. 1-2, 19F MRI images of sevofluran deposition in cranium (top) and trunk of a domestic pig. Uptake time: 40 minutes, measurement time: 32 minutes. 2D FLASH (no slice selection) matrix 64x128, FOV 300mm (top), 400mm(bottom).
Fig 3. Sevoflurane uptake kinetic detected by slice selective ^{19}F spectroscopy

Results

The time dependence of ^{19}F spectrum intensity, reflecting the servoflurane amount deposited in brain, is delayed and attenuated in comparison with the end-expiratory sevoflurane concentration (Fig 3).The distribution of the inhaled anesthetic (in this case sevoflurane) within the cranium and the trunk are depicted in Fig 1. Highest signal intensities and thus highest anesthetic concentrations were found in well blood-supplied, solid organs (brain, liver, kidney, heart). On the other hand, signal intensities within the lungs remain small, probably due to the fact that the lung is filled with gas in which the solubility of the sevoflurane is smaller (fat tissue-gas partition coefficient 30, muscle tissue-gas partition coefficient 2). The signal intensity distribution of the cranium image shows that the inhaled anesthetic is preferentially deposited in the brain. In the truncus image highest signal intensity was found in the liver having a peak signal-to-noise ratio (SNR) of 4.5 (pixel size 3.1x6.1mm), whereas in the cranium image the peak SNR=7.5 was found in the brain (at pixel size of 2.3mmx4.7mm)

Conclusion

The measurements confirm that in a 1.5T scanner 19F MRI/NMR is feasible for a large animal model. This imaging technique may open up a further understanding of fluorinated drugs, such as inhaled anesthetics. While the 19F MRI provides information about the spatial distribution of the fluorinated anesthetics, 19F NMR spectroscopy allows for assessment of regional kinetics as well as analysis of molecular interactions.

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References

Y. Xu, P. Tang, W. Zhang, L. Firestone, P. Winter, Fluorine-19 Nuclear Magnetic Resonance Imaging and Spectroscopy of Sevofluran Uptake and Elimination in Rat brain, Anaesthesiology, Vol 83(4), pp766-774, 1995.