Interference of Fluorinated Anesthesia on 19F MRS of Fluorinated Drug Metabolism in Liver

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Introduction: Fluorine (^{19}F) magnetic resonance spectroscopy (MRS) can monitor the concentration and metabolism of fluorinated cancer drugs like 5-fluorouracil (5-FU) and its oral prodrug capecitabine *in vivo* [1]. Previous ^{19}F MRS animal studies of capecitabine and 5-FU metabolism used a variety of anesthetic agents including injectable fluorinated compounds like Hypnovel and Hypnorm [2]. Fluorinated inhalation anesthesia agents like isoflurane are very useful in MRS animal studies since they allow long experimental acquisitions (hours) while most intravenous anesthetics last about 30 minutes/dose. Yet there is concern that ^{19}F spectra associated with fluorinated anesthesia (inhaled or injected) and their metabolites may interfere with the spectra from capecitabine and its metabolites. Therefore, we evaluated the effect of two common anesthetic agents, isoflurane and ketamine, on capecitabine liver metabolism in C57BL/6J mice using ^{19}F MRS to determine interference between anesthetic and therapeutic agent.

Methods: C57BL/6 mice were treated with 1250 mg/Kg capecitabine p.o. Animals were anesthetized with either isoflurane (2-3% induction and 1-2% maintenance) or ketamine (50 mg/Kg every 40 minutes) along with 1 LPM O_2. MRI and MRS were performed using a Bruker 7T/20 MRI running Paravision 4. The scanner was equipped with a dual-tuned 7 cm ID ^{1}H/^{19}F volume coil (Bruker) and a 15 mm ID detunable receive-only ^{19}F surface coil (Doty). A 5 mM NaF phantom was placed adjacent to the surface coil to aid in positioning the animal and aligning the spectra. The phantom were not used for signal normalization due to variations in positioning. ^{1}H MRI was used for positioning and shimming. ^{19}F spectra were acquired and averaged during 20 min blocks (2200 FIDs, TR: 0.5 s, spectral width: 60 kHz, points/FID: 890, flip angle: 60^0, RF pulse: 50µs) for 2 hours. The ^{19}F MRS data were analyzed using Bruker's Topspin application. The rate of capecitabine breakdown and the buildup of the intermediary molecules 5'dFCR/5'dFUR, 5-FU and FβAL were evaluated.

Results & Discussion: There were no significant differences between the capecitabine ^{19}F spectra obtained from C57BL/6 mice liver using isoflurane or ketamine (Fig. 1). However, the spectra acquired under ketamine had larger anabolite and catabolite concentrations (5'dFCR, 5'dFUR, and FβAL) at 120 minutes. This may be caused by higher liver metabolism under ketamine versus isoflurane. Less than 0.25% of inhaled isoflurane is metabolized by the liver [3] while ketamine is mainly metabolized in liver. Isoflurane is a respiratory depressant and may slow basal metabolism. We observed the respiration rate drop by 1/2-2/3 from ketamine to isoflurane. Therefore, the isolfurane experiments may need to be extended in duration to observe the same drug metabolism effects as ketamine.

In general, anesthesia can interfere with drug metabolism (rate) and/or drug spectra. Nevertheless, we did not observe spectral interference between either isoflurane or ketamine and capecitabine metabolites in the liver. Isoflurane allows rapid induction and recovery time. In contrast with injectable anesthesia, one can rapidly and easily respond to changes in animal state by changing the isoflurane levels. A catheter is required to readminister ketamine or the animal must be removed from the bore for periodic injections. We observed very long recovery times and effects from ketamine which may have been caused by excessive dosing or dose buildup.

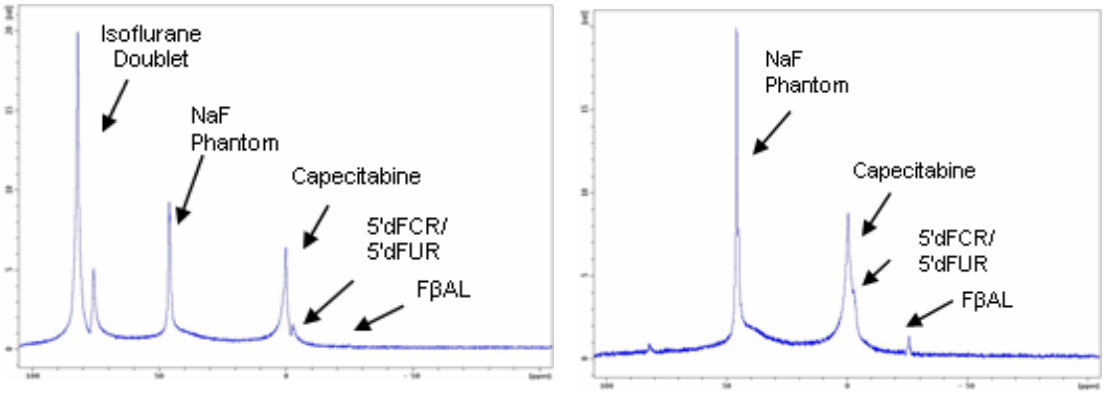

Figure 1: ^{19}F spectra acquired at 120 minutes post capecitabine administration using isoflurane (left) and ketamine (right) anesthesia. A trace peak from residual isoflurane in the oxygen line is observed in the spectra acquired with ketamine.

References: 1). Kamm YJK *et al*. British Journal of Cancer 2003 (89), 754-762. 2). Chung YL *et al.* Clin Cancer Res 2004 (10), 863-3870. 3). Hanusch C, *et al*. Methods 2007 (47), 68-78.