The Interaction of Gadolinium Based MR Contrast Agents with Choline

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INTRODUCTION

There is evidence to suggest that the presence of choline (Cho) in the spectrum of a breast lesion indicates malignancy (see for example [1]) . Typically localized proton MRS is performed after the administration of on an approved gadolinium contrast agent. There have been several papers describing the interactions of these agents with MR spectra in the brain [2-5] and in breast lesions [6]. In spite of the importance of this topic, there has been no systematic investigation of whether the magnitude of these effects depends on which contrast agent is employed. In this work we investigated the interactions of six different commercially available contrast agents; Dotarem, Magnevist, MutiHance, Omniscan, Optimark, and ProHance, both in vitro, and in an animal model for breast cancer.

MATERIALS & METHODS

MR Imaging and MR Spectroscopy: Data were acquired on 3.0 T GE Signa short bore twin speed system (GE Healthcare, Milwaukee, WI). The standard head coil was used for the in vitro studies. The animal studies were performed using a custom-built quadrature birdcage coil (6 cm diameter and 10 cm length). **In Vitro Studies**: We prepared a 250 ml solution containing 10 mM Cho at pH 7.2**.** MR spectra were acquired sequentially using the PRESS method from a 1x1x1 cm voxel with a TR of 2 sec and a TE of 144 msec, before and after serial additions of a solution containing 10 mm Cho and 250 mM of each of the six contrast agents. The T_2 was estimated from the line-width of the Cho peak. We also measured the T_1 of the Cho peak in each case using a progressive saturation method. **In Vivo Studies:** For each of the six contrast agents, data were acquired in 4 female Fischer 344 rats (250 – 300 gm) with a R3230 mammary adenocarcinoma implanted in the hind limb. Each animal was imaged using a T_1 weighted spin-echo sequence prior to, and after the tail vein injection of 0.1 mM/Kg of each agent. Localized MRS was acquired from a 1x1x1 cm voxel centered in the tumor using the PRESS method (TR of 2 sec; TE of 144 msec, and 256 averages), before and 15 minutes after injection of the contrast agent.

RESULTS

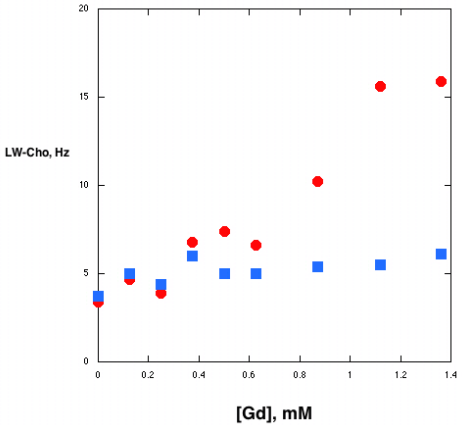

Figure 1. The variation in the line-width of choline with MultiHance (red) and Omniscan (blue) concentration.

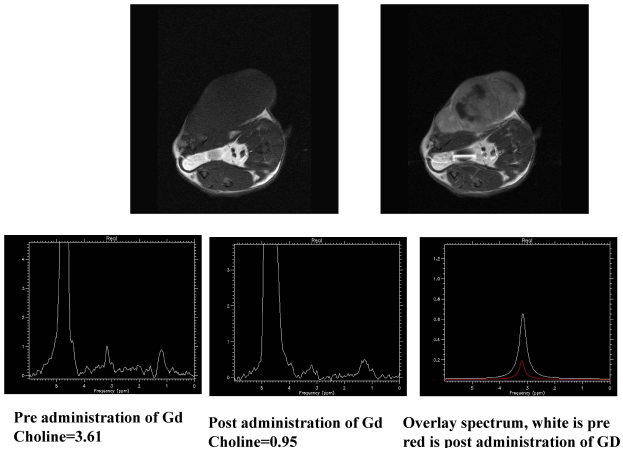

Figure 2. The in vivo MR spectra prior to (bottom left) and 15 min after injection of MultiHance (bottom middle). The pre and post MR images are shown above.

There were clear differences seen in the in vitro studies (see Figure 1). All of the negatively charged chelates increased the line-width and decreased the T_1 of Cho in a similar fashion. The neutral chelates had little or no effect. As an example of the results of the in vivo studies, Figure 2 shows that the administration of MultiHance (negatively charged) decreased the Cho signal in the spectrum obtained from the implanted tumor. The relative decrease is illustrated by the fitted spectra shown on the bottom right. All of the negatively charged agents showed similar behavior, while none of the neutral chelates had any appreciable effect on the Cho peak.

DISCUSSION

In 1977, Elgavish and Reuben [7] showed that a variety of methyl ammonium cations (like Cho) form an ion pair with a free carboxylate in the Gd(EDTA). The methyl groups are between 8-10 angstroms from the Gd leading to limiting line-widths of 30-180 Hz in the ion pair. We suggest that only the negatively charged contrast agents exhibit similar behavior, leading to a concentration dependent broadening of the Cho resonance in vitro. The situation in vivo is more complicated, since the Cho peak is thought to arise from molecules that are primarily intracellular and the contrast agents are thought to be primarily extracellular. Whatever the explanation, these results indicate that negatively charged contrast agents may have an effect on in vivo spectra of breast lesions and their use should be avoided in studies where MRS is added after to DCEMRI.

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