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The effect of Gd-DTPA on T_1-weighted choline signal in human brain tumours

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Abstract

The influence of Gd-DTPA on T_1-weighted (T_1W) proton MR spectra has been investigated in 19 patients with histologically verified low ($n = 13$) or high-grade ($n = 6$) gliomas. Repeat measurements were performed on 9 patients (7 low-grade and 2 high-grade), with 28 examinations performed in total. Comparison of spectra obtained before and after 0.2 mmol/kg Gd-DTPA showed contrast agent induced broadening of the choline signal without significant signal area change. Lack of enhancement of the choline signal with the T_1-weighted acquisitions implies that the contrast agent and the trimethylamine-containing species do not undergo significant direct interaction. Contrast agent induced changes in the choline signal observed in this and previous studies may, therefore, be attributable to T2*/susceptibility-based effects.

Keywords: Gd-DTPA; Choline; Glioma; ^{1}H-MRS

1. Introduction

The application of paramagnetic contrast agents to routine morphological and functional investigations is increasing. So too is ^{1}H-MRS, particularly in the study of neurological conditions such as neoplasia and neuro-degenerative disorders. In multifunctional studies combining MRS with MRI it may be beneficial to inject the contrast agent prior to spectroscopy to aid MRS voxel positioning. There is, however, potential for contrast agents to significantly affect quantitative spectroscopic investigations. *In vitro* experiments, for example, have shown Gd-DTPA to be more efficient at enhancing choline methyl proton relaxation than water relaxation [1].

In vivo studies have shown that using T_2W spectroscopy the choline peak area and line-shape are influenced by paramagnetic contrast agents [2,3]. In two studies [2,3] the paramagnetic contrast agent was reported to induce a mean loss of the choline peak area of 12 and 15% when using CSI PRESS (TE = 135 ms, TR = 1500 ms). The reports hypothesized that the induced changes by contrast agent were caused by an extracellular compound contributing to the choline signal coming into direct contact with the contrast agent. If the contrast agent induced signal changes result from a dipolar interaction with choline then the reduction in T_2 would be accompanied by a significant reduction in T_1 as predicted by *in vitro* experiments [1]. If the dipolar interaction is the mechanism by which contrast agents can perturb spectra then it could be validated by studying the effect on T_1W spectra. Since dipolar relaxation is proportional to r^{-6}, close proximity of the paramagnetic complex and target molecule is necessary to observe relaxation effects [4]. This is also true for T_2, but T_2^*/susceptibility induced perturbations do not require such close interactions. *In vivo*, the factor most likely to restrict metabolite-contrast agent interactions is cellular compartmentalization, i.e., the membrane inhibits intracellular metabolites from coming into contact with the extracellular contrast agent. With a T_2^*/susceptibility mechanism, however, the paramagnetic compound may cause perturbations of intracellular signals even when residing in the extracellular space.

The purpose of this study was two-fold: (i) to assess the detrimental influence double-dose contrast agent may have on the linewidth and peak area of short-echo time spectra obtained *in vivo* and (ii) to investigate the mechanism by which contrast agents can perturb spectra acquired *in vivo*.

The study therefore acquired T_1W single voxel spectra pre- and post-injection of double-dose (0.2 mmol/kg) Gd-

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DTPA in patients with histologically verified low- or high-grade gliomas. Both high- and low-grade tumour types were selected to provide tumours with varied post contrast enhancement and therefore intra-tumoural gadolinium concentrations. To obtain a measure of the influence of contrast agent on water relaxation within the spectroscopic voxel, T_1W unsuppressed water spectra were also recorded before and after the injection of Gd-DTPA. The percentage water enhancement within the localized volume was compared to the ^{1}H-MRS choline signal derived from the same volume. The water enhancement provides a measure of tumoural Gd-DTPA uptake.

2. Materials and methods

All data were acquired with a Siemens Vision 1.5T system (Siemens Medical Systems, Erlangen, Germany) using a standard circularly polarised head coil. The examination consisted of routine diagnostic imaging and a dynamic contrast enhanced protocol with spectroscopy performed pre- and post-administration of contrast agent. Double-dose (0.2 mmol/kg) contrast agent (Gd-DTPA, Magnevist (Schering Health Care Ltd., UK)) was injected as a bolus through a peripheral line using a MEDRAD power injector (Medrad UK Ltd., Schering Healthcare Ltd., UK).

2.1. Spectroscopy

Single voxel ^{1}H-MR spectra were acquired using STEAM localization. The voxel (volume between 8 and 15.6 cm^3) was positioned within the tumour, judged by axial FLAIR (TR = 9000 ms, TE = 99 ms, flip angle = 180°) and coronal Turbo Spin-Echo (TR = 5400 ms, TE = 99 ms, flip angle = 180°) images. A global shim was performed, followed by manual shimming using the STEAM sequence with the water suppression pulse voltages set to zero. CHESS water suppression was then optimized manually. T_1W water suppressed spectra (TR = 888 ms, TE = 20 ms, nt = 64) were acquired before and approximately 13 minutes after injection of the contrast agent. T_1-weighted spectra with the CHESS pulse voltages set to zero provided water spectra (TR = 888 ms, TE = 20 ms, nt = 4) and were acquired immediately after the pre- and post-contrast metabolite spectra. Prior to acquiring the post-contrast spectra, parameters were re-loaded and checked as necessary. These parameters included the frequency, pulse voltages and the shim currents.

2.2. Patient recruitment

All patients in the study had histologically verified low (n = 13) or high-grade (n = 6) gliomas and had not received radiotherapy or surgical intervention at least 6 months prior to the MR examination reported here. Repeat examinations were performed on 7 low-grade and 2 high-grade glioma patients following intervals of at least ten weeks. In total 20 analyses of low-grade tumours were performed and 8 of high-grade tumours.

2.3. Data analysis

All spectra were fitted with Lorentzian lineshapes using the VARPRO (VARiable PROjection) algorithm from within MRUI (Magnetic Resonance User Interface) 96.3. In order to quantify the Gd-DTPA uptake, the pre- and post-contrast T_1W water signal intensities were included in the equation below. The enhancement within the voxel, expressed as a percentage, was designated the intravoxel enhancement (IVE).

$$\%IVE = \left(\frac{T1W_{post} - T1W_{pre}}{T1W_{pre}} \right) \times 100$$

3. Results

Typically, spectra from low-grade tumours exhibited high choline levels relative to creatine, low NAA and variable lipid signals. Other metabolites exhibiting broad resonances or poor signal to noise were observed. They were, however, not consistently identifiable.

Pre- and post-contrast T_1W spectra from a high-grade glioma are shown in Fig. 1a and 1b, respectively. The spectra are typical of short-echo time spectra from high-grade gliomas, demonstrating high choline levels (relative to creatine) and large methylene and methyl lipid peaks. A slight broadening in the choline linewidth was apparent post-contrast, with the lipid and creatine signals remaining unchanged. Although the choline peak height was reduced post-contrast, the peak area remained constant.

The relationship between the intravoxel enhancement and the choline linewidth is shown in Fig. 2. A progressive increase in the choline linewidth as the voxel water enhancement increases is apparent. The grouping of points at low IVE values arises from the low-grade tumours which typically do not exhibit contrast agent uptake. An R value of 0.82 and $p < 0.0001$ indicates significant linear correlation. There was no significant linear correlation between the choline peak area and the IVE indicating no T_1 derived signal enhancement ($R = 0.32$, $p > 0.05$) of choline.

Spectra acquired from high-grade gliomas demonstrated a mean choline linewidth change of +3.9 Hz (SD = 2.8 Hz), whereas for the low-grade gliomas the mean change was 0.1 Hz (SD = 1.2 Hz).

4. Discussion

Contrast agent induced changes in the choline signal have previously been observed in the brain using T_2W spectroscopy [2,3]. The proposed mechanism for the change

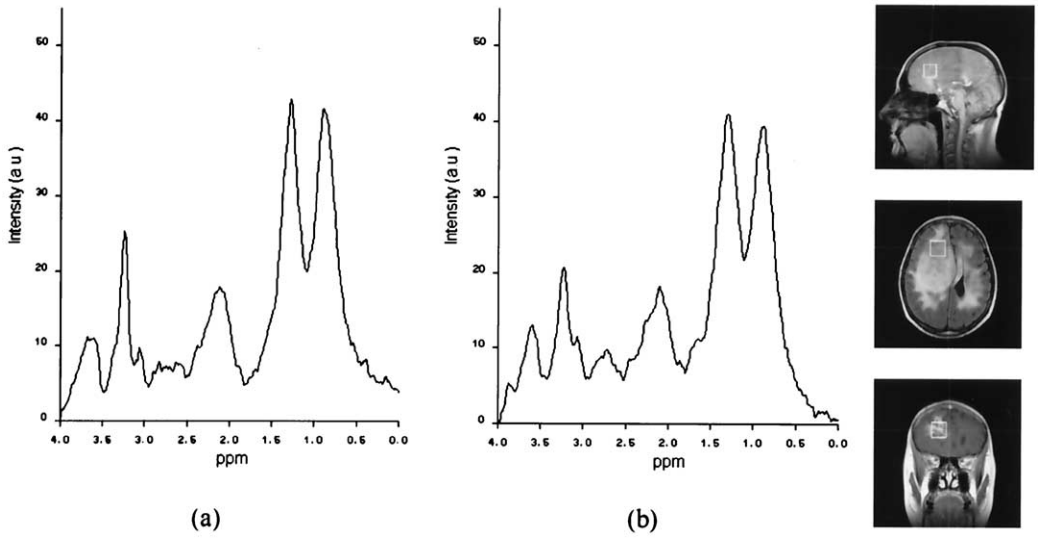

Fig. 1ab. Short echo time T_1W spectra obtained pre (a) and post (b) administration of double-dose Gd-DTPA are presented. There is a slight signal broadening of the choline resonance with associated loss in peak height. The lipid methyl and methylene resonances appear unchanged after administration of the contrast agent.

was a reduction in the T_2 of extracellular metabolite. If a reduction in the T_2 of extracellular choline occurs then it follows from previous *in vitro* studies that the T_1 should also be enhanced [1]. To test the proposed hypothesis, T_1W spectra were acquired before and after administration of double dose contrast agent. Signal enhancement as a consequence of gadolinium induced T_1 reduction would suggest a direct interaction in the extracellular space between contrast agent and metabolite. The effect of T_2 derived signal intensity modulation was minimized by the short echo time used. Creatine and NAA signals were often not quantifiable in the higher grade tumours making analysis over the range of tumour grades not possible. As a result, this study in common with previous studies, has focused on the choline peak.

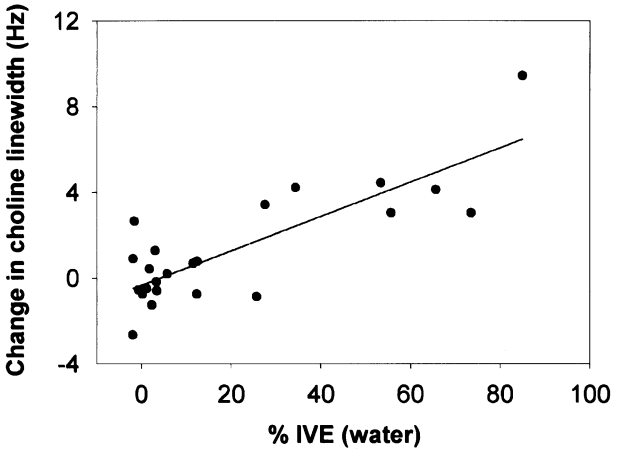

Fig. 2. The choline linewidth plotted against water enhancement represented by the intravoxel enhancement (IVE). A significant linear correlation is observed ($R = 0.82$, $p < 0.0001$). The IVE in all the measurements from high-grade gliomas is greater than 20%, indicating a significant extravascular concentration of Gd-DTPA in these tumours. This is associated with an increased choline linewidth measured 13 minutes post injection of the contrast agent.

To determine the extent of contrast agent induced enhancement of water within the spectroscopic voxel, T_1W water spectra pre- and post-contrast were acquired. This approach has the benefit of obtaining a measure of the gadolinium concentration reaching the spectroscopic voxel. Furthermore, this simple, rapid approach enables the acquisition of data from the same voxel as the metabolite spectra, facilitating direct comparison between the water and metabolite data. The acquisition of water data immediately after the metabolite data minimizes errors due to the dynamics of the contrast agent. Enhancement of the water signal within the spectroscopic voxel is, however, dependent upon the initial T_1 of the tissue and therefore the IVE value will only reflect the intra-voxel gadolinium concentration.

The correlation of IVE value with choline linewidth clearly shows that choline, as measured by short echo time ^{1}H-MRS in brain tumours, is influenced by the presence of paramagnetic contrast agent. Theoretically, contrast agents could affect the MR measured signal via (i) direct interaction within the extracellular space resulting in dipolar relaxation, (ii) by inducing T_2^*/susceptibility derived relaxation of intracellular metabolite from the extracellular space and (iii) T_2^*/susceptibility effects caused by contrast agent remaining in the intact vasculature.

Firstly, it is important to consider the contrast agent kinetics as this will dictate the location of the contrast agent at the time at which post-contrast spectroscopy is undertaken. In the current study, MRS was performed before and ~3 minutes after bolus injection of the contrast agent. At

this time point there will no longer be a bolus concentration contained in the vasculature. The latter mechanism is therefore unlikely to contribute to the spectroscopically observed changes. Secondly, the low-grade non-enhancing gliomas typically possess an intact blood brain barrier and therefore would only give rise to an intravascular derived susceptibility effect. As the choline signal linewidth is unaffected in the low-grade tumours this mechanism is unlikely to contribute significantly to the perturbation of the choline signal. It is known that the contrast agent used here does not enter into cells but remains in the interstitial space prior to washout from the tumour. In enhancing tumours therefore the contrast agent must exert an effect on metabolites whilst residing in the extracellular space. If the choline resided too in this extracellular space then it would be expected that a T_2 change (indicated by line-broadening or signal loss at long echo time) would be accompanied by a change in T_1. As no signal enhancement was seen with these T_1-weighted acquisitions this interaction is not occurring. The contrast agent therefore must exert its effect from the extracellular space without coming into close contact with the choline. This indicates that the extracellular contrast agent is perturbing metabolite nuclei within the cell and therefore strongly suggests a susceptibility mechanism.

The fact that Sijens et al. [2,3] only observed a decrease in choline could be due to sensitivity issues, i.e., changes in the order of 15% were only quantifiable in the largest peak which is likely to be choline in brain tumours at TE = 135 ms. This mechanism also shows that both short and long echo time spectra can be satisfactorily acquired post-contrast in low-grade tumours possessing an intact blood brain barrier.

In high-grade tumours, where a significant concentration of Gd-DTPA is present in the extravascular space, signal loss will only occur at long-echo time. At short echo time as in this study only signal broadening may be detected. This may consequently hinder accurate peak fitting in spectra which commonly already suffer from peak overlap.

5. Conclusion

Significant gadolinium induced changes in the choline peak linewidth have been observed in brain tumours. A possible mechanism for this is a T_2^*-susceptibility induced relaxation of an intracellular choline pool, evidenced by changes in the linewidth without change of intensity in T_1 weighted spectra. With a long echo time as used by Sijens et al. [2,3], it is likely that the T_2^*-susceptibility effects would result in signal loss due to a faster transverse magnetization decay. Undertaking spectroscopy post-contrast at short echo time will not directly perturb the choline peak area. However, the broadening of resonances due to T_2^* enhancement may hinder accurate peak fitting and subsequent quantification.

Acknowledgments

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