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Protocol design for high relaxivity contrast agents in MR imaging of the CNS

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Abstract Numerous experimental and clinical studies have shown that the use of the high relaxivity MR contrast agent MultiHance (gadobenate dimeglumine, Gd-BOPTA; Bracco Imaging, Milan, Italy) results in improved detection, delineation and enhancement of CNS tumors compared to other available gadolinium agents. This leads not only to more confident diagnoses, but also to a substantially improved differential diagnostic process. The higher R1 and R2 relaxivities of MultiHance, deriving from the weak and transient interaction of the Gd-BOPTA contrast-effective moiety of this agent with serum albumin, help also to further optimize functional MR imaging techniques such as perfusion MRI and dynamic MR an-

giography. However, because the interaction between the Gd-BOPTA chelate and serum albumin affects proton relaxation times, imaging parameters need to be adapted to achieve maximum benefit from the high relaxivity of MultiHance at different magnetic field strengths. In this article we review the unique MR imaging properties of MultiHance for the assessment of brain tumors and other cerebral pathologies, and give practical information on how best to optimize MR sequence parameters to achieve the optimal contrast between normal CNS tissue and lesion.

Keywords Contrast agents · MRI · MultiHance · Central nervous system (CNS)

Introduction

Magnetic resonance (MR) imaging is the modality of choice for imaging the central nervous system (CNS) [1–3]. For most CNS diseases the use of contrast-enhanced MRI is mandatory for diagnosis and appropriate patient work-up, including presurgical planning and postsurgical follow-up.

To be able to detect and accurately assess the dimensions of CNS lesions requires high lesion-to-brain/spine contrast. The inherent lesion-to-brain/spine contrast on native MR scans is frequently insufficient for accurate depiction of lesions. Augmentation of the contrast on MR is achieved with the use of gadolinium-based contrast agents which cross the blood–brain barrier at sites

of disruption or compromise [4]. The MR contrast agents widely used for detection and diagnosis of CNS disease include Magnevist (Gd-DTPA, gadopentetate dimeglumine; Schering/Berlex), ProHance (Gd-HP-DO3A, gadoteridol; Bracco), Omniscan (Gd-DTPA-BMA, gadodiamide; Amersham Health), Optimark (Gd-DTPA-BMEA, gadoversetamide; Tyco), Dotarem (Gd-DOTA, gadoterate meglumine; Guerbet) and Gadovist (Gd-DO3A-butrol, gadobutrol; Schering). Despite differences in molecular structure and physicochemical properties [5] these agents have similar R1 and R2 relaxivity values [6–8] and thus demonstrate similar contrast-enhancing performance when administered at equivalent doses [9–13]. Typically, these “first generation” MR contrast agents are administered at a standard dose of 0.1 mmol/kg body weight although numerous

studies have shown that CNS lesion detection may be improved with the use of higher doses [14–23] and/or dedicated sequences [23, 24].

MultiHance (Gd-BOPTA, gadobenate dimeglumine; Bracco Imaging, Milan, Italy) possesses markedly higher R1 and R2 relaxivities at all field strengths compared to the agents listed above [6–8] due to weak, transient interactions of the Gd-BOPTA contrast-effective moiety with serum albumin [25, 26]. Several studies have demonstrated that the increased R1 relaxivity of MultiHance leads to significant improvements in lesion contrast enhancement, lesion delineation and visualization of lesion vascularity and internal morphology when administered at a standard dose of 0.1 mmol/kg body weight [27–30]. Studies have also shown that the increased R2 relaxivity of MultiHance might have benefits for T2*-weighted perfusion imaging [31, 32].

However, the studies performed to date comparing MultiHance with conventional “first generation” agents have all utilized imaging protocols optimized for use with standard agents that do not interact with serum proteins. The capacity of MultiHance to interact with serum albumin implies that optimal imaging performance might be achieved by modifying the sequence parameters slightly in order to take account of the unique properties of this agent [33]. In the present article the relaxation properties of MultiHance are summarized and appropriate sequence modifications to fully utilize the imaging potential of this agent are suggested.

R1 and R2 relaxivity

Recently, Pintaske et al. [8] performed an *in vitro* study to determine the relaxivity values of MultiHance, Magnevist and Gadovist in human plasma at magnetic field strengths of 0.2, 1.5 and 3 T. Based on relaxivity measurements made over a range of contrast agent concentrations between 0.001 and 16 mmol/l, MultiHance was shown to produce markedly higher R1 and R2 relaxation rates and r_1 and r_2 relaxivities at all magnetic field strengths when compared to both Magnevist and Gadovist. Higher field strengths resulted in lower R1, R2, and r_1 values for all contrast agents and lower r_2 values for Magnevist and Gadovist. Whereas a linear dependence of R1 and R2 on contrast agent concentration was found for Magnevist and Gadovist, a nonlinear dependence for MultiHance was observed for concentrations greater than 1 mM, reflecting the capacity of the Gd-BOPTA moiety for protein interaction. The r_1 and r_2 relaxivity values of MultiHance increased with decreasing concentration.

In another recent *in vitro* study Giesel et al. [26] measured the r_1 and r_2 relaxivity values of the same three contrast agents in human plasma containing various concentrations of human serum albumin (HSA) be-

tween 0 and 7 g/dl. Each contrast agent was evaluated at a standard concentration of 0.5 mmol/l and at a magnetic field strength of 1.5 T. In the HSA concentration range of 0 and 7 g/dl, Magnevist and Gadovist showed relative increases in relaxation rates of approximately 13% and 22% for R1 and 26% and 30% for R2, respectively (Fig. 1). Conversely, the relative increases in relaxation rate with MultiHance were approximately 108% and 363% for R1 and R2, respectively. Over the physiological range of HSA concentrations (3.5–5.5 g/dl) an increase in R1 relaxivity of 39% was noted for MultiHance compared to 8% and –4% for Magnevist and Gadovist, respectively. The corresponding increases in R2 relaxivity over the physiological range of HSA

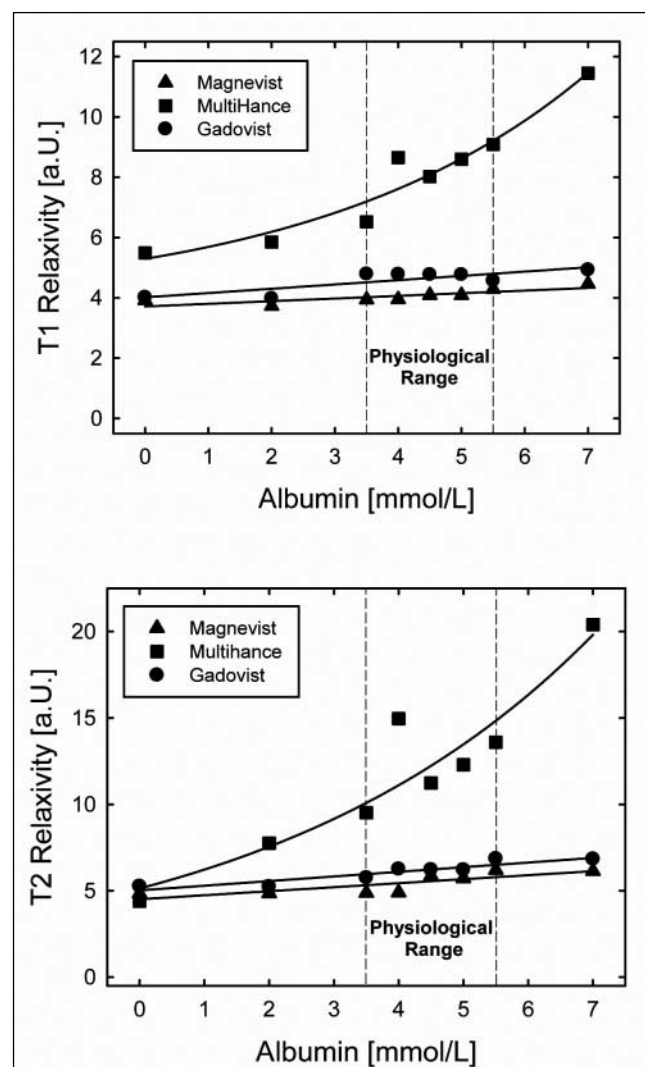


Fig. 1 *In vitro* measurements of the T1- and T2-relaxivity values of Magnevist, Gadovist and MultiHance at 1.5 T. Within the physiological range of albumin (3.5–5.5 mmol/l) MultiHance has twice the r_1 - and r_2 -relaxivity than 0.5 M Magnevist and 1 M Gadovist

concentrations were 42% for MultiHance, 27% for Magnevist and 19% for Gadovist. Molecular modeling analyses in this study revealed that approximately ten small hydrophobic pockets exist on the HSA surface into which the unique benzyloxymethyl group of the Gd-BOPTA chelate can fit. These interactions between the Gd-BOPTA moiety and HSA result in stronger noncovalent binding than occurs between HSA and either Magnevist or Gadovist resulting in an overall slowing of the tumbling rate of the Gd-BOPTA chelate and thus an increase in relaxation rate.

Protocols for the use of MultiHance in CNS disease

Sequence parameters

Although the almost double r_1 relaxivity of MultiHance at all magnetic field strengths confers substantial benefits for MR imaging of the CNS using established T1-weighted sequence parameters [27–30], little has yet been done to determine whether modification of the sequences would result in improved imaging performance. A recent preliminary investigation has revealed that while MultiHance provides substantially more signal at any given TR and TE compared to conventional agents, greater differences between the agents are achieved by shortening the TR and TE and by increasing the flip angle [33]. Shorter TR and TE values give a stronger T1 weighting on both spin echo (SE) and gradient echo (GRE) sequences which is beneficial for contrast-enhanced imaging. The scan time also correlates directly with the length of the TE, especially for GRE sequences since more slices can be obtained in a given TR interval. MultiHance provides the same enhancement at TE val-

Table 1 Mean contrast enhancement of MultiHance and Gadovist at different TE values in an intraindividual comparative study on 14 patients

TE (ms)	MultiHance	Gadovist	P value
20	182±60	184±125	n.s.
12	233±68	146±82	0.0068

Table 2 Mean lesion-to-white matter contrast for MultiHance and Gadovist at different TE values in an intraindividual comparative study on 14 patients

TE (ms)	MultiHance	Gadovist	P value
20	218±76	231±93	n.s.
12	218±76	231±93	n.s.

ues from 20 ms to as short as 12 ms. Conversely, the enhancement from other gadolinium agents drops off between 20 and 12 ms (Tables 1 and 2, Fig. 2). For this reason, MultiHance may help compensate for any loss of signal intensity that occurs when fast imaging sequences are used with short TE. This may be of particular importance in the case of 3D GRE sequences used for volumetric studies (such as tumor volume assessments for treatment planning) or for time-resolved sequences in which the inflow of contrast agent provides the relevant diagnostic information.

The TR also plays a significant role in the contrast enhancement between white matter and cerebral tumors. In order to be effectively T1-weighted, imaging sequences should have a TR comparable to the T1 relaxation time of the tissue. Normally a TR of 500–700

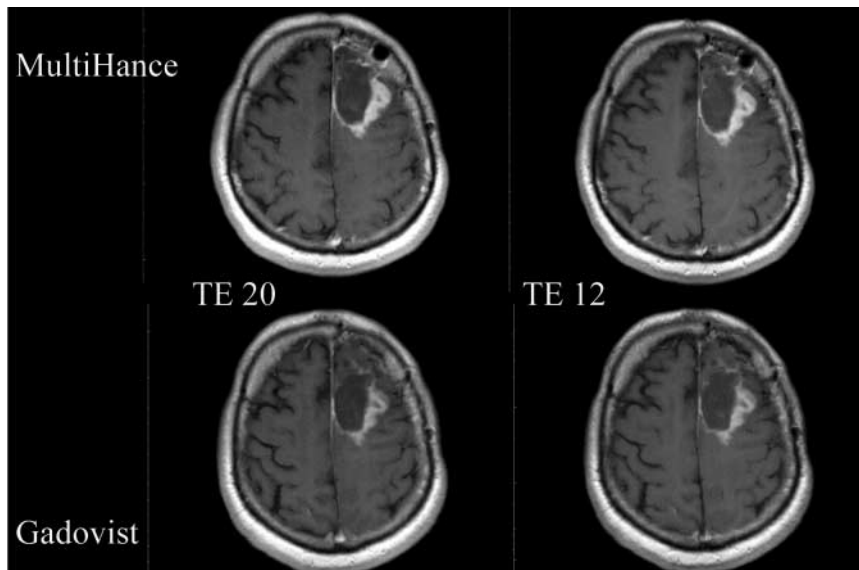


Fig. 2 Intraindividual comparative study MultiHance and Gadovist at different TE values. For both values of TE MultiHance provides a stronger enhancement and a better delineation of the lesion from the surrounding tissue. The difference is more pronounced at short TE measurements

ms is used for most T1-weighted SE sequences. The TR is varied according to the desired slice coverage required to cover the whole head in a single measurement. However, the optimal TR for each contrast agent is different and should be further evaluated to allow a better adaptation of the imaging parameters. If the optimal TR is too low to permit complete coverage one should consider other options to increase the number of slices, e.g. parallel imaging or imaging with slice gaps.

Field strength

The contrast enhancement effect in clinical MR imaging is also dependent on the field strength of the MR system and improves with increasing field strength up to and including 3 T. An obvious consequence of field strength dependence is that significantly lower levels of contrast enhancement are obtained with low field strength (0.2–0.7 T) systems. The contrast enhancement achieved on these low-field systems when a recommended dose of 0.1 mmol/kg body weight of conventional gadolinium contrast agent is used is frequently insufficient for adequate diagnostic imaging. In this context the higher relaxivity of MultiHance may significantly improve the achievable contrast enhancement relative to that achieved with other available agents.

In the same way, the greater relaxivity of MultiHance is also advantageous on higher field strength systems between 1.0 T and 3.0 T. Although most studies have thus far been conducted at 1.0 or 1.5 T, preliminary studies

have demonstrated equivalent benefits of MultiHance for CNS imaging at 3 T [34, 35].

Increasing the field strength also changes the relaxation times of the tissue which requires further adaptation of both TR and TE. Although T2 relaxation times tend to be independent of the external magnetic field strength, the T1 relaxation times of tissues increase with increasing field strength. On the other hand the r1 relaxivity of contrast agents decrease with increasing magnetic field strength. Several studies have shown that higher doses of contrast agent are needed at low field to achieve the same contrast enhancement achieved with a standard dose of contrast agent at 1.5 T [36–38]. However, few studies have yet been performed to establish the optimum sequence parameters for individual contrast agents at different magnetic field strengths.

Summary

MultiHance is a valuable contrast agent for the assessment of CNS disease. It has higher relaxivity and has proven to be significantly superior to standard gadolinium agents in all clinical studies conducted to date, both in terms of qualitative subjective assessments and quantitative objective measurements of signal intensity. The use of MultiHance can compensate the reduced signal intensity enhancement and signal loss that is characteristic of sequences with short TE. The advantages of MultiHance over conventional gadolinium agents are evident at all magnetic field strengths.

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