Macrocyclic MR contrast agents and r1 relaxivity: are there tangible differences?

By Dr. Matthew J Kuhn, Dr. Julia W Patriarche & Dr. Miles A Kirchin

Gadolinium-based contrast agents (GBCAs) work by shortening the T1, T2, and T2* relaxation time constants of adjacent water protons in tissues. The greater the T1 shortening the greater the signal enhancement obtained on T1-weighted images. The extent to which T1 is shortened, and hence the effectiveness of a specific GBCA in clinical practice, depends on the local tissue concentration of the GBCA and on its specific r1 relaxivity. The higher the r1 relaxivity of the GBCA the greater the extent to which T1 is shortened and the greater the signal enhancement obtained. This means that for a given equivalent approved GBCA dose of 0.1 mmol/kg bodyweight, a GBCA with higher r1 relaxivity will improve the visualization of lesions and potentially allow better detection of small or poorly enhancing lesions compared to that achieved with GBCAs having standard relaxivity [1].

The best way to directly compare GBCAs for their ability to shorten T1 relaxation times and enhance image contrast is by means of blinded, randomised, intra-individual crossover studies in which each patient undergoes two MRI examinations under identical conditions, one with one GBCA and the other with the comparator GBCA. Numerous intra-individual crossover studies have unequivocally and unanimously demonstrated significantly improved contrast enhancement and imaging performance for gadobenate dimeglumine (MultiHance; Bracco) compared to all other GBCAs across a range of applications, including CNS [2-6]. This is to be expected given the markedly higher r1 relaxivity of this GBCA [6-11; Figure 1]. MultiHance, however, while approved and widely used in the USA and elsewhere for extra-hepatic indications including CNS [12], is approved in Europe solely for contrast-enhanced MRI of the liver. The only GBCAs currently approved in Europe for CNS and other extra-hepatic indications are the macrocyclic GBCAs gadoteridol (ProHance; Bracco), gadobutrol (Gadovist; Bayer) and gadoterate meglumine (Dotarem; Guerbet/Clariscan; GE), and questions remain as to whether the reported differences in r1 relaxivity among these GBCAs are sufficient to elicit tangible differences in contrast enhancement. For example, intra-individual crossover studies that compared Gadovist with other macrocyclic GBCAs have produced conflicting findings with some authors reporting significantly better enhancement and imaging performance with Gadovist compared to comparator agents [13-15] while others, comparing the same GBCAs under identical conditions, reported similar or non-inferior imaging performance for the comparator GBCA compared to Gadovist [16, 17]. Invariably, authors that report better imaging performance with Gadovist [13-15] ascribe the stated benefits to the two-fold higher concentration of the Gadovist formulation and to higher r1 relaxivity of the gadobutrol molecule, often describing gadobutrol as a "high relaxivity macrocyclic agent" [18, 19].

Until recently, all intra-individual crossover comparisons of GBCA performance have utilized a subjective approach to image evaluation in which contrast enhancement and efficacy determinations are based on the subjective assessments of blinded readers. Thus, qualitative assessment of images (e.g., of lesion border delineation, disease extent, visualization of lesion internal morphology, lesion enhancement compared with surrounding normal tissue) have typically been performed by three experienced readers in blinded fashion and scored using 3-point Likert scales (e.g., from –1 [examination 1 superior] through 0 [examinations equal] to +1 [examination 2 superior]). Likewise, quantitative evaluations have relied on the subjective placing of regions-of-interest (ROI) on homogenous areas within lesions

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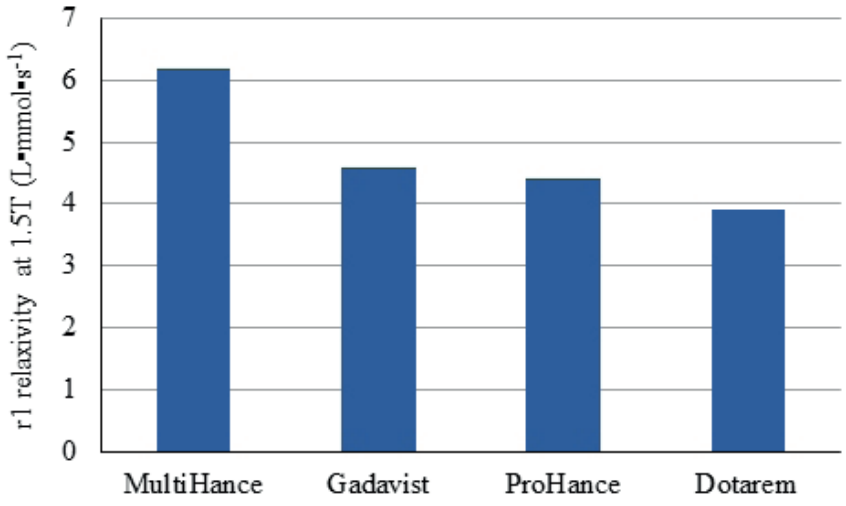

Figure. 1. r1 relaxivity values of group II GBCAs as classified by the American College of Radiologists [ref 12]. Adapted from Shen et al 2015 [ref. 10].

and normal brain tissue that avoid vessels, necrotic areas and other visibly inhomogeneous structures or artifacts. Although image randomization and anonymization as well as strict care in the evaluation of images may help to overcome many potential issues related to subjective nature of image assessment, these strategies do not help to overcome the inherent limitations of the human visual system which is not designed to easily identify differences between images when compared side-by-side. Because the human visual system works in abstractions, it suppresses our sensitivity to differences when images are displayed side-by-side. As demonstrated recently (20), new artificial intelligence/machine learning (ML) software provides opportunities to look at enhancement characteristics quantitatively, in an entirely objective manner, enabling greater clarity, reliability, and reproducibility of interpretations.

ARTIFICIAL INTELLIGENCE/ MACHINE LEARNING

Unlike traditional quantitative analysis which relies on volumetric assessment of voxels in a given ROI (i.e., by simply calculating the number of voxels in the user-defined ROI), the dedicated AI software ("Change Detector"; A.I. Analysis, Inc.) described in detail previously [20] utilizes multiple forms of artificial intelligence (expert systems, fuzzy logic)/machine learning (genetic algorithms) in concert to construct Quantitative Enhancement Maps (QEM) in which imaging features unrelated to GBCA-induced enhancement are separated from features that indicate enhancement. Once an initial ROI is positioned to encompass the entire lesion(s), the software performs a pipeline of processing steps on the pre-contrast and contrast-enhanced T1-weighted images from each paired data set corresponding to each patient. By making calculations of enhancement in nuanced terms (i.e., by rating the degree of enhancement within each voxel automatically and reproducibly on a fuzzy membership scale of 0.0 [nonenhancing] to 1.0 [maximally enhancing]), the Quantitative Enhancement Analysis (QEA) system provides a per-ROI sum of enhancement that is not only an expression of the spatial extent of an enhancing region but also the degree of enhancement within that region. Comparison of the QEM for an acquisition made with one GBCA with the QEM for an acquisition made with another GBCA permits accurate interpretation of the differential enhancement achieved with different GBCAs. Since the QEMs have reproducibly rated the degree of enhancement on a voxel-by-voxel basis throughout both acquisitions using a 0.0 (no enhancement) to 1.0 (maximal enhancement) scale, this is accomplished simply by subtracting one QEM (from the first agent) from the other QEM (from the other agent) providing a quantitative map of the differences in enhancement on a voxel-by-voxel basis on a scale of -1.0 (greatest possible decrease in enhancement from agent A to agent B) to 0.0 (no difference in enhancement between agent A and agent B) to +1.0 (greatest possible increase in enhancement from agent A to agent B). This map of differences in enhancement can be displayed as a standalone volume or superimposed as a color map on another volume.

Figure 2 shows a representative case from an intra-individual crossover comparison of ProHance versus Gadovist [16] for brain tumor imaging. The conventional contrast-enhanced T1-weighted spin-echo images acquired with gadoteridol and gadobutrol suggest similar contrast efficacy for these two GBCAs which is confirmed using change detector AI software, which shows that the median difference in enhancement (-0.01) is within the pre-defined Zone of Equivalence.

CONCLUSIONS

The importance of relaxivity as the key indicator of MR contrast agent efficacy has been demonstrated in a large series of intraindividual comparative studies in MRI. The application of AI software can confirm and strengthen radiological results of properly designed and powered studies in demonstrating when numerical differences in relaxivity can be translated into clinical advantage. As stated by Kanal *et al* [1]: "High

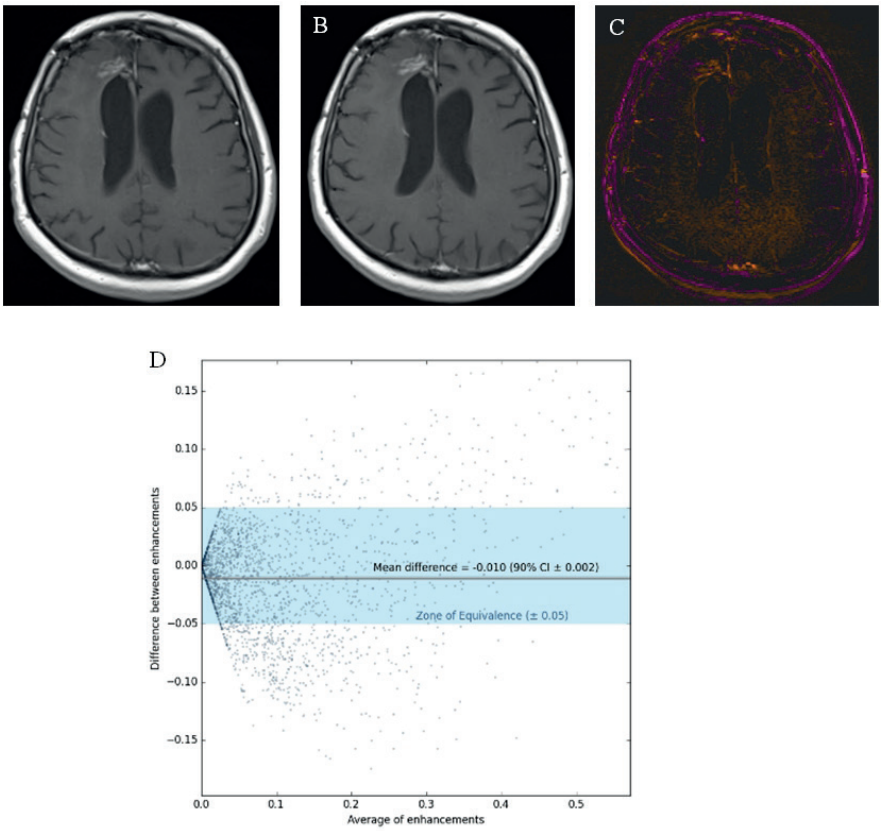

Figure 2. 39-year old male, 136 kg, with oligoastrocytoma grade III and previous brain surgery (craniotomy and tumor excision) imaged on a Siemens Avanto 1.5 T scanner. Conventional contrast-enhanced T1-weighted spin-echo images acquired after 0.1 mmol/kg (13.6 mL) Gadovist (A) and, 3 days later, 0.1 mmol/kg (27.2 mL) ProHance (B). The QE change map (C) reveals regions that differ in enhancement between the two exams. The mean difference in signal enhancement is clearly within the equivalence zone on the Bland-Altman chart (D) indicating equivalent signal enhancement.

relaxivity" should be defined not numerically alone, but rather by an objectively proved ability of an agent to deliver increased clinical utility as measured by clinically relevant increases in signal enhancement (rather than merely small but statistically significant signal increases) or, preferably, an objectively measured increase in lesion number or lesion extent compared with other "standard" GBCAs". As confirmed using dedicated AI software, the minimal differences in r1 relaxivity amongst the currently available macrocyclic GBCAs are insufficient for any to be considered a high relaxivity GBCA. Newer genuinely "high relaxivity" macrocyclic GBCAs are currently in development [21].

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