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Commentary

Optimal Use of MR Contrast Agents: How Much Is Enough?

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The use of contrast agents combined with clinical MR imaging is still relatively new. While gadolinium chelate contrast agents such as gadopentetate dimeglumine (Magnevist) share many similar biophysical properties with the well-understood iodinated CT contrast agents, it is necessary to point out that there are some important differences. One characteristic that is unique to MR contrast agents is the paradoxical loss of signal intensity that occurs at high concentrations of paramagnetic agents due to marked shortening of the T2 relaxation time. This T2 effect becomes dominant and overshadows the increased signal that would normally be produced by the shortened T1 relaxation time. It is this characteristic of paradoxical signal loss that is the subject of the preceding article by Yousem et al. [1], which suggests that such T2 shortening effects from contrast material may be observable under certain circumstances at the standard clinical dosage of gadopentetate dimeglumine of 0.1 mmol/kg. These T2 shortening effects are potentially very important since, in the absence of toxicity, they help to define the effective upper limit of paramagnetic contrast agent that should be used. Beyond this level, signal intensity in a lesion will be decreased and lesions may be misinterpreted or missed entirely.

Yousem and co-workers describe a series of cases in which they observe an apparent decrease in lesional signal intensity on postcontrast T1-weighted images. Retrospective analysis of region of interest (ROI) measurements also suggests a decrease of signal intensity that averages approximately 10% within these lesions. These investigators theorize that this apparent decrease in signal intensity may be the result of an additive effect between the paramagnetic properties of the gadolinium chelate and hemoglobin or melanin proteins.

If the authors' explanation is correct, then this would represent an important finding that contains many implications for the correct use of contrast agents and for establishing the optimal or maximal dosage of contrast agent for cerebral MR studies. Although we currently use a dose of 0.1 mmol/kg of gadopentetate dimeglumine, the optimal dose is not yet defined. Some investigators have suggested that a lower dose (0.05 mmol/kg) may be sufficient, although anecdotal data suggest that this dose may not enhance all lesions (Yuh et al., paper presented at the annual meeting of the RSNA, 1990). Other investigators [2] have suggested that use of a higher dose of contrast agent would improve enhancement and would help to detect small lesions or lesions that enhance only mildly, thus increasing the sensitivity of contrast-enhanced MR. Currently, there are ongoing clinical studies by at least two different groups evaluating the safety and efficacy of gadolinium chelates at dosages as high as 0.3 mmol/kg (A. Nichol, Sterling Pharmaceuticals, and T. Lucas, Squibb, Inc., personal communication). If the results of Yousem et al. are corroborated, then such higher doses are unwarranted since they will, in some cases, decrease sensitivity of the contrast-enhanced MR study for the reasons already cited. However, before we abandon all investigation of higher doses of contrast agent, we must first take a critical look at the report in question, since there are several unanswered questions raised by this investigation.

This article is a commentary on the preceding article by Yousem et al.

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Since the observations of decreased lesional intensity were made retrospectively, the MR scan parameters were not controlled, thus precluding optimal data analysis. Different TRs and TEs were used between cases and, in some instances, different parameters were used on the pre- and postcontrast T1-weighted images. There was no control for MR system transmit or receiver attenuations and no reference standard was present within the scanning field of view to correct for differences in amplification and scaling of the MR signal. Furthermore, if shortened T2 relaxation time is the factor responsible for the apparent signal decrease, then one would expect this effect to be most pronounced on T2-weighted images. However, only one patient in their series had T2-weighted imaging performed after contrast enhancement, and although this patient showed a mild decrease in calculated T2 relaxation time following contrast administration, one must be cautious about extrapolating the results from one case. Other factors might account for this apparent decrease in T2 value, such as differences in sampling technique (i.e., ROI placement), slight patient motion between scans with varying partial volume effects, and so on.

In the absence of a true reference standard, the investigators compared signal intensity within the lesion to that of CSF, gray matter, and white matter on the pre- and postcontrast images. While this normalization technique is the best that could be done in a retrospective study, it contains an inherent error due to a small, visually imperceptible enhancement of these tissues after contrast administration. Measurements of gray and white matter under controlled conditions in animals [3, 4] as well as in humans [5] have demonstrated slight decreases in T1 relaxation time and resulting increases in brain parenchymal signal intensity that measure approximately 4–7% above baseline precontrast values. Thus, small increases in gray and white matter tissue intensity may provide an alternative explanation, other than a decrease in T2 relaxation time, for the changes in calculated signal intensity ratios between brain tissue and lesion.

While CSF may seem to provide a better internal control than brain tissue, this also presents problems in reliability and reproducibility. Since CSF has very low signal intensity on T1-weighted images, the resulting signal-to-noise ratio of ventricular CSF is low. In addition, pulsatile motion of CSF further decreases the reliability of this measurement. Finally, a recent report (Knutzon et al., paper presented at the annual meeting of the Association of University Radiologists, Orlando, March 1991) evaluated CSF signal intensity before and after contrast enhancement in an animal model. The results of this study demonstrated a slight decrease in T1 relaxation time and a resultant increase in CSF signal intensity following IV injection of gadopentetate dimeglumine. This presumably occurs as a result of leakage of contrast agent into the CSF from the choroid plexus.

Also of importance is the fact that no prior documented clinical cases of T2 shortening effects from IV administration of contrast material have been reported. Brant-Zawadzki et al. [6] described a single anecdotal case in which they observed "disappearance" of a multiple sclerosis lesion on a postcontrast study. They suggested that this might have been caused by T2 shortening effects from the contrast agent. However, this experience has not, to date, been corroborated, and partial volume effects might also account for this change. It is curious that Yousem and co-workers observed this phenomenon predominantly in pituitary tumors, which generally do not demonstrate the highest degrees of contrast enhancement. Other lesions, such as hypervascular primary brain tumors, metastases, and meningiomas, which are frequently observed to enhance intensely, have not shown similar effects. At our own center, we conducted a study comparing T1- *and* T2-weighted images obtained both before and after contrast enhancement in a series of 21 patients with 25 enhancing lesions to determine if there were advantages or disadvantages to obtaining long TR images after contrast administration [7]. Several of the lesions in our study enhanced intensely and a few had associated intralesional hemorrhage. In none of our cases did we observe a decreased signal intensity on postcontrast T2-weighted images when compared with the precontrast long TR images.

To postulate that there is an addition of T2 shortening effects from blood or melanin and exogenously administered paramagnetic contrast agents presumes that sufficient amounts of the paramagnetic contrast agent can enter the hemorrhagic portion of the lesion and that the paramagnetic contrast molecules can closely approach those same hydrogen protons that are being affected by the hemoglobin or melanin proteins. This is doubtful, and there is no evidence to date to support this hypothesis. Because of the retrospective nature of these cases, the data are insufficient to prove or disprove the possibility that T2 shortening effects from the paramagnetic contrast agent may be responsible for the apparent decrease in lesional signal intensity. For the reasons already cited, I feel that this explanation is seriously in doubt.

What other factors can explain the phenomenon that is observed? The most likely possibility, that the authors themselves raise, is that of differences in scaling of the images before and after contrast enhancement due to differences in receiver gain that creates the appearance of diminished lesional signal intensity. However, even if scaling factors are the responsible culprits, the observations that are made have important clinical implications. First of all, the radiologist performing the MR study must be aware that image scaling factors change following IV injection of paramagnetic contrast agents and may produce the false impression of diminished signal intensity within a nonenhancing or minimally enhancing lesion upon initial observation of the images. Second, this scaling effect is magnified severalfold when combining postcontrast T1-weighted images with a frequency-selective, presaturation fat-suppression technique. Fat-saturation techniques are commonly used to evaluate intraorbital lesions, lesions at the base of the skull, and tumors of the extracranial head and neck. Great caution must be exercised if, as may often be the case, one compares precontrast T1-weighted images without fat saturation to postcontrast T1-weighted images obtained with a fat-saturation technique. Because of suppression of high signal from adjacent or surrounding fat, nonenhancing lesions may be falsely interpreted as demonstrating enhancement on the postcontrast images. To elimi-

nate any ambiguity, at least one comparable sequence should be obtained before and after contrast injection (i.e., matched T1-weighted images in the same plane before and after contrast, both obtained either with or without a fat-saturation pulse).

Finally, the article by Yousem and colleagues should serve as an important reminder that, irrespective of toxicity, there is an upper limit to the amount of paramagnetic contrast agent that can be administered, beyond which the T2 shortening effects may cause a paradoxical loss in signal intensity and lead to misinterpretation. The clinical dose at which this phenomenon occurs has not been established. Clearly, further investigation is needed in this important area and careful scrutiny of data from high-dose clinical trials of gadolinium chelate contrast agents should help to answer this question. In the meantime, the radiologist is once again reminded that there are important differences between MR contrast agents and iodinated CT contrast agents. Optimal dose as well as optimal pulse sequence combinations for efficient and effective clinical utilization are still to be defined. We do not yet fully understand all of the idiosyncrasies of paramagnetic MR contrast agents, but a thorough knowledge of their basic principles and mechanisms of action is required of the MR specialist to avoid potential pitfalls in interpretation.

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