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Comparative Studies of Different Gadolinium Agents in Brain Tumors: Differences between Gadolinium Chelates and Their Possible Influence on Imaging Features

N. Anzalone

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COMMENTARY

Comparative Studies of Different Gadolinium Agents in Brain Tumors: Differences between Gadolinium Chelates and Their Possible Influence on Imaging Features

In recent years, there have been a number of studies comparing different gadolinium chelates for MR imaging of tumors, particularly for MR imaging of intracranial neoplasms. These have included intraindividual studies that compared gadobenate dimeglumine (MultiHance; Bracco, Milan, Italy) with other gadolinium agents[1-3] for imaging cerebral tumors, and a study similar to that of Kim et al[4] that compared gadobutrol (Gadovist; Bayer Schering Pharma, Berlin, Germany) with gadopentetate dimeglumine (Magnevist; Bayer Schering Pharma) for imaging of cerebral metastasis.[5]

Studies comparing gadobenate dimeglumine with other gadolinium chelates have demonstrated the superiority of this agent in terms of contrast enhancement and lesion characterization, delineation, extension, and definition of internal structures at 1.5T and 3T. Lesions included were mostly intracranial tumors, with the highest percentage being intraparenchymal gliomas. Although detailed evaluation of different histologic types has yet to be performed, the superiority of gadobenate dimeglumine has been shown across all lesions, including gliomas, meningiomas, lymphomas, and metastases.

The 2 studies[4,5] that compared gadobutrol with gadopentetate dimeglumine revealed greater enhancement and a higher rate of lesion depiction in favor of gadobutrol. These data support the fact that gadolinium contrast agents are different and that these differences potentially have important diagnostic implications.

A number of gadolinium-containing contrast agents are currently available for use in MR imaging of the central nervous system. These include gadobenate dimeglumine, gadobutrol, gadodiamide (Omniscan; Nycomed Amersham, Oslo, Norway), gadofosveset trisodium (Vasovist; Epix Pharmaceuticals, Lexington, Massachusetts), gadopentetate dimeglumine, gadoterate meglumine (Dotarem; Guerbet, Aulnay-sous-Bois, France), gadoteridol (ProHance; Bracco), and gadoversetamide (OptiMar; Mallinckrodt, St. Louis, Missouri).

Gadolinium contrast agents can be classified by the molecular structure of their gadolinium-chelate complex—macrocyclic or linear—and by being ionic or nonionic.

Related to the structure is compound stability, with a demonstrated increased stability and consequently lower propensity to release gadolinium ions for macrocyclic agents.[6] Release of gadolinium ions, which are toxic, is thought to be relevant to the development of nephrogenic systemic fibrosis (NSF).[7]

Most currently available gadolinium-containing contrast agents are formulated at a concentration of 0.5 mol/L, while gadobutrol is formulated at a higher concentration of 1.0 mol/L.

In an animal model of glioma, gadolinium concentration in the mass after gadobutrol injection has been shown to be higher than that after injection of other gadolinium chelates.[8] Although not confirmed clinically, this could theoretically have an impact on brain lesion signal-intensity enhancement. In the case of gadobutrol, the increased gadolinium concentration per unit volume is considered a possible factor added to the T1 shortening effect.[9]

A physicochemical property of contrast agents that is relevant to imaging performance is relaxivity. This property defines the ability of an agent to alter tissue relaxation rates. A higher T1 relaxivity leads to greater T1 shortening and thus to greater lesion enhancement. The relaxation effect has been demonstrated at different field strengths. Whereas the relaxivity is lower at higher field strengths, the relative differences between agents are maintained or even increased. Different gadolinium agents have different relaxivity values and among these differences gadobenate dimeglumine and gadobutrol have higher relaxivity values, with a higher value for gadobenate dimeglumine.

Although there is consensus on the diagnostic benefits of gadolinium agents in MR imaging, there is less consensus on how best to use them to optimize lesion visualization.

One of the possible variables is the dose of the contrast agent. The standard dose of gadolinium for MR imaging of the central nervous system is 0.1 mmol per kilogram of body weight. However studies investigating different pathologies, including brain tumors and metastases, indicate that lesion detection may be improved with higher concentrations (0.2–0.3 mmol/Kg).[10] Thus, many centers, like that of Kim et al,[4] use double doses in their routine screening protocols. Frequently, higher doses may be given in cases of diagnostic doubt following the standard 0.1-mmol/Kg dose. Unfortunately, NSF has been related to higher doses of gadolinium, and current recommendations are to use the lowest dose possible to achieve diagnosis.

The timing of image acquisition is another way to optimize lesion contrast enhancement, but as yet, there is little evidence to suggest that it changes with different gadolinium compounds.

To date, all published intraindividual comparative studies have shown significant differences in MR imaging features between the 2 gadolinium agents compared, but none have directly addressed the potential clinical impact of these results. In large part, this is due to the difficulty in evaluating clinical impact end points within the confines of a relatively small patient population.

From most of the studies, it can be concluded that if a lesion enhances to a greater extent, it is better delineated from the surrounding normal structure and can be better characterized. As a result, radiosurgical target volumes can be better defined; this targeting leads to easier resection with less likelihood of tumor recurrence. However, specific outcome studies are needed to look at specific lesion features that may influence treatment or outcome.

The principal interest in the study by Kim et al[4] is that they have looked at the number of secondary lesions, an important consideration influencing both treatment and outcome.

Comparative intraindividual studies of different gadolinium compounds have contributed to our knowledge that gadolinium contrast agents are different because they can show

different imaging characteristics; the way they do it is not completely explained, though relaxivity and concentration both play a role. Moreover the recently described correlation between some gadolinium chelates and NSF adds another important factor to the relevance of this difference.

Although no clear distinct clinical impact has been demonstrated by these comparative studies, they can be an important step in understanding the behavior of MR imaging contrast media and in better targeting their clinical indications.

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N. Anzalone
Department of Neuroradiology
Scientific Hospital S Raffaele
Milan, Italy

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