AJNR

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

N. Anzalone

AJNR Am J Neuroradiol 2010, 31 (6) 981-982
doi: https://doi.org/10.3174/ajnr.A2068
http://www.ajnr.org/content/31/6/981

rather than use the closure device, you would instead pay me $200 dollars to do the manual compression for you, with just 8 cases per day, I could make $8000 in a 5-day work week. If I only took 2 weeks of vacation, I could earn $400,000 annual pretax income. That is pretty good money to do minimally skilled manual labor. With significant time between cases for coffee breaks, I would have to seriously consider such a position if it were offered. Another way to think of it is that manual compression is no more difficult than delivering a pizza, and few of us would pay someone $200 to deliver a pizza. Seriously, if you are going to defend the use of closure devices by citing a decreased need for labor, you must consider that $200 can buy a lot of labor.

So why are so many physicians compulsively attracted to expensive arterial closure devices? Is it the time savings that they offer to the physician? I personally see very little time savings. A closure device in a typical case probably takes about 5 minutes of operator time to deploy, and often there is a small amount of bleeding requiring a short period of compression after the device is deployed. So, perhaps 5 or 10 fewer minutes are spent at the patient's side. If someone other than the physician could be doing the manual compression, then the device is actually adding nonreimbursable physician time. Is it the added safety to the patient? There is no reason to believe that there is safety improvement,[4] except perhaps in occasional patients with coagulopathy or requiring anticoagulation. The real reasons that percutaneous closure devices are so widely used may be the following: 1) the simple love of gadgets that is characteristic of most interventionalists, and 2) a disdain of the boredom of the 15 minutes of manual compression (this disdain is exacerbated by remembrances of local legendary cases from the past when manual compression efforts went on for an hour or more). The physician gets to play with an ingenious gadget rather than suffering the boredom and cramped hands associated with manual compression. Aggressive marketing undoubtedly has a role, but I think that the marketing is playing to the physician's natural attraction to the devices rather than generating the attraction.

In the end, individual physicians and institutions must do their own assessment of the proper role of percutaneous closure devices. I can only hope that such assessments are performed rationally.

References

1. McTaggart R, Raghavan D, Haas R, et al. **StarClose vascular closure device: deployment and re-access in a neurointerventional radiology practice.** *AJNR Am J Neurodiol* 2010;31;1148–50
2. Turi ZG. **Vascular closure devices.** In: Heuser RR, Henry M, eds. *Textbook of Vascular Interventions.* 2nd ed. London: Infoma UK; 2008:168
3. Global Vascular Closure Device Markets: U.S., Europe, Rest of World. July 2008. http://www.researchandmarkets.com/research/642582/global_vascular_cl. Accessed October 13, 2009
4. Koreny M, Riedmuller E, Nikfardjam M, et al. **Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis.** *JAMA* 2004;291:350–57
5. Logemann T, Luetmer P, Kaliebe J, et al. **Two versus six hours of bed rest following left-sided cardiac catheterization and a meta-analysis of early ambulation trials.** *Am J Cardiol* 1999;84:486–88
6. Doyle BJ, Konz BA, Lennon RJ, et al. **Ambulation 1 hour after diagnostic catheterization: a prospective study of 1009 procedures.** *Mayo Clin Proc* 2006;81:1537–40

H.J. Cloft
Senior Editor

DOI 10.3174/ajnr.A1990

EDITORIAL

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.

References

1. Maravilla KR, Maldijan JA, Schmalfuss IM, et al. **Contrast enhancement of central nervous system lesions: multicenter intraindividual crossover comparative study of two MR contrast agents.** *Radiology* 2006;240:389–400
2. Rowley HA, Scialfa G, Gao P-Y. **Contrast-enhanced MR imaging of brain lesions: a large-scale intraindividual crossover comparison of gadobenate dimeglumine versus gadodiamide**. *AJNR Am J Neuroradiol* 2008;29:1684–91. Epub 2008 Jul 3
3. Rumboldt Z, Rowley HA, Steinberg F, et al. **Multicenter, double-blind, randomized, intraindividual crossover comparison of gadobenate dimeglumine and gadopentetate dimeglumine in MRI of brain tumors at 3 tesla.** *J Magn Reson Imaging* 2009;29:760–67
4. Kim ES, Chang JH, Choi HS, et al. **Diagnostic yield of double-dose gadobutrol in the detection of brain metastasis: intraindividual comparison with double-dose gadopentetate dimeglumine.** *AJNR Am J Neuroradiol* 2010 Jan 28 [Epub ahead of print]
5. Anzalone N, Gerevini S, Scotti R, et al. **Detection of cerebral metastasis on magnetic resonance imaging: intraindividual comparison of gadobutrol with gadopentetate dimeglumine.** *Acta Radiol* 2009;50:933–40
6. Sieber MA, Lengsfeld P, Frenzel T, et al. **Preclinical investigation to compare different gadolinium-based contrast agents regarding their propensity to release gadolinium in vivo and to trigger nephrogenic systemic fibrosis-like lesions.** *Eur Radiol* 2008;18:2164–73. Epub 2008 Jun 11
7. Grobner T. **Gadolinium: a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis?** *Nephrol Dial Transplant* 2006;21:1104–08
8. Le Duc G, Corde S, Charvet AM, et al. **In vivo measurement of gadolinium concentration in a rat glioma model by monochromatic quantitative computed tomography: comparison between gadopentetate dimeglumine and gadobutrol.** *Invest Radiol* 2004;39:385–93
9. Huppertz A, Roher M. **Gadobutrol, a highly concentrated MR- imaging contrast agent: its physicochemical characteristics and the basis for its use in contrast-enhanced MR angiography and perfusion imaging.** *Eur Radiol* 2004;14:12–18
10. Uysal E, Erturk SM, Yildirim H, et al. **Sensitivity of immediate and delayed gadolinium-enhanced MRI after injection of 0.5 M and 1.0 M gadolinium chelates for detecting multiple sclerosis lesions.** *AJR Am J Roentegenol* 2007;188:697–702

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

DOI 10.3174/ajnr.A2068