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EDITORIAL

The New Restrictions on the Use of Linear Gadolinium-based Contrast Agents in Japan

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Kanda et al.[1] first reported in 2014 that high signal intensity in the dentate nucleus on T_1-weighted images (T_1WI), a finding previously attributed to multiple sclerosis[2] or irradiation,[3] correlated with the number of past gadolinium-based contrast agent (GBCA) administrations.[4–6] Animal and human studies have found that linear GBCAs cause much greater brain deposition of gadolinium than macrocyclic GBCAs.[7–13] In November 2017, the package inserts of GBCAs in Japan were revised, with the addition of two recommendations: 1) careful consideration as to restricting GBCA use to clinical circumstances in which the information provided by the contrast is necessary, and 2) the use of macrocyclic GBCA is a primary choice and a linear GBCA is used when the use of a macrocyclic GBCA is not adequate because of a history of adverse effects (gadoxetic acid, a linear GBCA used for hepatobiliary imaging, is an exception). This revision was due to the results of studies on gadolinium deposition in the brain after linear GBCA administration, which has been a worldwide topic of discussion.[5,6]

In the current Japanese market, both linear and macrocyclic GBCAs are available. The linear GBCAs include gadodiamide, gadopentetate dimeglumine, and gadoxetic acid, and the macrocyclic GBCAs include gadobutrol, gadoteridol, and gadoterate meglumine. The above-mentioned revision means that gadodiamide and gadopentetate dimeglumine can be used only in patients who had adverse effects from macrocyclic GBCAs. Gadoxetic acid is also a linear GBCA, but it contains only 25% of the gadolinium concentration found in other GBCAs. However, gadolinium accumulation in the brain due to gadoxetic acid administration has been confirmed with MRI.[14] As there is no hepatobiliary GBCA besides gadoxetic acid, it will remain the first choice for hepatobiliary MRI.

There will be much discussion on the selection of GBCAs. Macrocyclic GBCA has great advantage in their stability while, despite evidence of greater brain deposition, linear GBCA has been used safely for long a time. However, even using macrocyclic GBCAs, small degree of accumulation in the dentate has been shown in rats[15] and in humans after 37–44 times administrations.[16] The degree of accumulation of gadolinium differs slightly among macrocyclic GBCAs, but the differences in accumulation are much smaller than the differences between linear GBCAs and macrocyclic GBCAs.[17,18]

Linear GBCAs have been in use for nearly 30 years, with the only reported major adverse event being nephrogenic systemic fibrosis (NSF). A suspected association of parkinsonism and GBCA has been disproven.[19] A study of human fetal exposure that did not make a distinction between linear and macrocyclic GBCAs did note an increased risk of inflammatory/rheumatic skin diseases, as well as of stillbirths and neonatal deaths.[20] Although there is a report that fetal mice exposed to 100 doses of linear GBCAs showed behavioral abnormalities, this is an unrealistic exposure in daily clinical practice.[21] Taken together, given that accumulation of linear GBCAs have had no adverse effects outside of NSF for nearly 30 years, the risk of gadolinium accumulation can be sufficiently reduced by using macrocyclic GBCAs.

In 2017, linear GBCAs have been the topic of much discussion. The European Medicines Agency's, Pharmacovigilance Risk Assessment Committee has recommended the removal of linear GBCAs from the market because of the gadolinium deposition in the brain.[22] On the other hand, the American College of Radiology and the US Food and Drug Administration (FDA) announced that they would not restrict the use of linear GBCAs.[23,24] In December 2017, FDA issued a new statement, but there is no new restriction of GBCA usage, and suggested that the kind of GBCA used should be carefully selected in high-risk patients, that is, those likely requiring multiple lifetime doses, pregnant women, children,

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and patients with inflammatory conditions.[25] The restrictions on linear GBCAs are totally different in Europe, America, and Japan, because it is still unclear whether or not the gadolinium accumulation in the brain is toxic. Health care professionals should pay close attention to the latest research results and decide which GBCA to use based on their own policies. In Japan, linear GBCA use has drastically decreased from 64.7% in 2014 to 24.7% in 2016,[26] and it is predicted that usage will show further decrease because of this revision in the package insert. Although the risk of adverse effects due to gadolinium deposition in the brain is not proven, the use of linear gadolinium has been restricted in this revised package insert in view of the risk of possible adverse effects in the future. I believe that the changes to the Japanese package insert reduce the risk to the patient.

Conflicts of Interest

The author declares that there is no conflict of interest.

References

1. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 2014; 270:834–841.
2. Roccatagliata L, Vuolo L, Bonzano L, Pichiecchio A, Mancardi GL. Multiple sclerosis: hyperintense dentate nucleus on unenhanced T1-weighted MR images is associated with the secondary progressive subtype. Radiology 2009; 251: 503–510.
3. Kasahara S, Miki Y, Kanagaki M, et al. Hyperintense dentate nucleus on unenhanced T1-weighted MR images is associated with a history of brain irradiation. Radiology 2011; 258:222–228.
4. Errante Y, Cirimele V, Mallio CA, Di Lazzaro V, Zobel BB, Quattrocchi CC. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. Invest Radiol 2014; 49:685–690.
5. Kanda T, Oba H, Toyoda K, Kitajima K, Furui S. Brain gadolinium deposition after administration of gadolinium-based contrast agents. Jpn J Radiol 2016; 34:3–9.
6. Kanda T, Nakai Y, Oba H, Toyoda K, Kitajima K, Furui S. Gadolinium deposition in the brain. Magn Reson Imaging 2016; 34:1346–1350.
7. Kanda T, Osawa M, Oba H, et al. High signal intensity in dentate nucleus on unenhanced T1-weighted MR images: association with linear versus macrocyclic gadolinium chelate administration. Radiology 2015; 275:803–809.
8. Radbruch A, Weberling LD, Kieslich PJ, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 2015; 275:783–791.
9. Jost G, Lenhard DC, Sieber MA, Lohrke J, Frenzel T, Pietsch H. Signal increase on unenhanced T1-weighted images in the rat brain after repeated, extended doses of gadolinium-based contrast agents: comparison of linear and macrocyclic agents. Invest Radiol 2016; 51:83–89.
10. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 2015; 275:772–782.
11. Kanda T, Fukusato T, Matsuda M, et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. Radiology 2015; 276:228–232.
12. Murata N, Gonzalez-Cuyar LF, Murata K, et al. Macrocyclic and other non-group 1 gadolinium contrast agents deposit low levels of gadolinium in brain and bone tissue: preliminary results from 9 patients with normal renal function. Invest Radiol 2016; 51:447–453.
13. Robert P, Lehericy S, Grand S, et al. T1-weighted hypersignal in the deep cerebellar nuclei after repeated administrations of gadolinium-based contrast agents in healthy rats: difference between linear and macrocyclic agents. Invest Radiol 2015; 50:473–480.
14. Kahn J, Posch H, Steffen IG, et al. Is there long-term signal intensity increase in the central nervous system on T1-weighted images after MR imaging with the hepatospecific contrast agent gadoxetic acid? A cross-sectional study in 91 patients. Radiology 2017; 282:708–716.
15. McDonald RJ, McDonald JS, Dai D, et al. Comparison of gadolinium concentrations within multiple rat organs after intravenous administration of linear versus macrocyclic gadolinium chelates. Radiology 2017; 285:536–545.
16. Bjørnerud A, Vatnehol SAS, Larsson C, Due-Tønnessen P, Hol PK, Groote IR. Signal enhancement of the dentate nucleus at unenhanced MR imaging after very high cumulative doses of the macrocyclic gadolinium-based contrast agent gadobutrol: an observational study. Radiology 2017; 285:434–444.
17. Bussi S, Coppo A, Botteron C, et al. Differences in gadolinium retention after repeated injections of macrocyclic MR contrast agents to rats. J Magn Reson Imaging 2018; 47:746–752.
18. Lohrke J, Frisk AL, Frenzel T, et al. Histology and gadolinium distribution in the rodent brain after the administration of cumulative high doses of linear and macrocyclic gadolinium-based contrast agents. Invest Radiol 2017; 52:324–333.
19. Welk B, McArthur E, Morrow SA, et al. Association between gadolinium contrast exposure and the risk of parkinsonism. JAMA 2016; 316:96–98.
20. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association between MRI exposure during pregnancy and fetal and childhood outcomes. JAMA 2016; 316: 952–961.
21. Khairinisa MA, Takatsuru Y, Amano I, et al. The effect of perinatal gadolinium-based contrast agents on adult mice behavior. Invest Radiol 2018; 53:110–118.
22. PRAC concludes assessment of gadolinium agents used in body scans and recommends regulatory actions, including suspension for some marketing authorisations. www.ema.

europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/03/news_detail_002708.jsp&mid=WC0b01ac058004d5c1 (Accessed: Nov 25, 2017).
23. ACR response to the European PRAC recommendations www.acr.org/About-Us/Media-Center/Press-Releases/2017-Press-Releases/20170404-ACR-Response-to-the-European-PRAC-Recommendations (Accessed: Nov 25, 2017).
24. FDA drug safety communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue. www.fda.gov/Drugs/DrugSafety/ucm559007.htm (Accessed: Nov 25, 2017).
25. FDA drug safety communication: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings. www.fda.gov/Drugs/DrugSafety/ucm589213.htm (Accessed: Jan 27, 2018).
26. Mugikura S, Takase K. Fear of linear gadolinium-based contrast agents and the Japanese radiologist's choice. Jpn J Radiol 2017; 35:695–696.