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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.

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