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Macrocyclic GBCA again shows less signal intensity in kids

By Wayne Forrest, AuntMinnie.com staff writer

February 2, 2018 -- A study from Germany in the February issue of *Investigative Radiology* found that the use of a linear gadolinium-based contrast agent (GBCA) resulted in increased signal intensity in two brain regions in pediatric patients, compared with the use of a macrocyclic GBCA.

While the findings resemble previous research on pediatric and adult patients, these results come from comparisons of linear and macrocyclic GBCAs among two similar groups of children and adolescents. In addition, no subject had received MRI contrast before enrollment in the trial, nor chemotherapy and/or irradiation of the brain, which has been linked to T1 hyperintensity in the dentate nucleus -- a common location for gadolinium accumulation.

"Our investigation is also the first publication that compared effects in the dentate nucleus and the globus pallidus after repeated applications of the macrocyclic MRI contrast medium gadobutrol versus the linear agent gadopentetate dimeglumine in children and adolescents in one study," said lead author Dr. Diane Renz from Jena University Hospital. "We observed a significant T1-weighted signal increase of the dentate nucleus and the globus pallidus after serial injections of gadopentetate dimeglumine, but not after repeated gadobutrol administrations."

GBCA and hyperintensity

Several studies have explored the association between GBCA exposure and signal intensity on subsequent unenhanced MRI scans. The brain's dentate nucleus and globus pallidus regions appear particularly prone to gadolinium retention, leading to T1 hyperintensities. Increases in T1-weighted signal intensity have been found after repeated administrations of linear contrast agents, but not after injections of macrocyclic GBCAs.

> "Macrocyclic MR contrast media are more stable than linear agents, as the macrocyclic molecules form a ring system in which gadolinium ions are caged, whereas the linear less-stable chelates wrap around the gadolinium ions," Renz wrote in an email to *AuntMinnie.com*. "Thus, linear MR contrast media are more prone to release free gadolinium ions, which seems to be responsible for the intracranial gadolinium depositions."

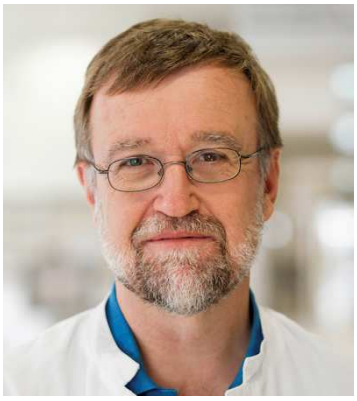
Dr. Diane Renz from Jena University Hospital.

Naturally, one much-discussed question is how the accumulation of gadolinium could affect the development of a child's brain. Pediatric brain development begins in "fetal life and proceeds continuously into adolescence with continual myelination and proliferation of synapses," explained senior author Dr. Hans-Joachim Mentzel, also from Jena University Hospital.

In October 2017, Tibussek et al observed a lack of increased signal intensity in the brains of pediatric patients who received macrocyclic GBCAs, compared with subjects who were not exposed to contrast. The findings suggested no retention or accumulation of gadolinium, even after multiple macrocyclic GBCA-enhanced MRI scans.

In a May 2017 study, McDonald et al confirmed the presence of gadolinium deposits in postmortem brain tissue of pediatric patients with normal renal function who underwent linear GBCA-enhanced MRI scans.

"Due to its ongoing development, the pediatric brain is specifically vulnerable to toxin exposures," Mentzel said. "Thus, any medication and contrast medium application should be specifically judged in children and adolescents."



Dr. Hans-Joachim Mentzel from Jena University Hospital.

For their study, Renz, Mentzel, and colleagues enrolled a total of 53 children who underwent consecutive GBCA-enhanced MRI brain scans over a period of 13 years on a 1.5-tesla device (Magnetom Avanto or Magnetom Sonata, Siemens Healthineers; Achieva, Philips Healthcare). One group of 28 subjects (mean age, 8.4 ± 6.8 years) received at least three injections of the linear GBCA gadopentetate dimeglumine (Magnevist, Bayer HealthCare). A second group of 25 subjects (mean age, 9.7 ± 5.4 years) received at least three injections of the macrocyclic GBCA gadobutrol (Gadovist, Bayer) (*Invest Radiol*, February 2018, Vol. 53:2, pp. 119-127).

To quantify signal intensity changes in the dentate nucleus, the researchers calculated ratios of the dentate nucleus to the pons and to the middle cerebellar peduncle (MCP). The group also calculated the globus pallidus-to-thalamus ratio.

Linear vs. macrocyclic

Renz and colleagues found that after three administrations of the linear gadopentetate dimeglumine agent, the T1-weighted signal intensity ratios increased on a statistically significant basis. By comparison, the signal intensity ratios for the macrocyclic GBCA gadobutrol remained relatively flat with no significant change after three or more administrations.

Comparison of signal intensities (SI) from brain regions based on GBCA

				p-value*

	Mean SI ratio before GBCA	Mean SI ratio after 3 GBCA administrations	Mean SI ratio difference	
Dentate nucleus-to-pons ratio				
Gadopentetate dimeglumine	0.991 ± 0.040	1.027 ± 0.034	0.036 ± 0.031	< 0.001
Gadobutrol	0.992 ± 0.048	0.997 ± 0.041	0.005 ± 0.029	0.367
Dentate nucleus-to-MCP ratio				
Gadopentetate dimeglumine	0.980 ± 0.047	1.014 ± 0.046	0.034 ± 0.032	< 0.001
Gadobutrol	0.981 ± 0.050	0.986 ± 0.051	0.005 ± 0.033	0.439
Global pallidus-to-thalamus ratio				
Gadopentetate dimeglumine	1.018 ± 0.028	1.043 ± 0.029	0.025 ± 0.025	< 0.001
Gadobutrol	1.021 ± 0.032	1.023 ± 0.030	0.002 ± 0.024	0.733

**p-values < 0.05 are statistically significant.*

While the clinical effect of the T1 hyperintensities remains unclear, Renz and Mentzel said clinicians at Jena University Hospital only use macrocyclic GBCAs.

"Nevertheless, we judge thoroughly if the application of an MRI contrast medium is justified in a specific case and provides additional relevant information," Renz said. "Application of contrast media should not be part of strict MRI protocols in children and adolescents; rather, each contrast medium administration should be assessed with caution, including the analysis of benefit versus possible adverse and negative effects."

The use of macrocyclic GBCAs instead of linear agents is in accordance with current guidelines and recommendations from the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency and the European Society of Paediatric Radiology, Renz added.

The researchers plan to investigate in a long-term follow-up whether intracranial T1 hyperintensities might result in neurologic and psychologic impairment. These associations are challenging to evaluate in a valid study design, but they would have a high clinical impact, Mentzel said.

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