Gadolinium Contrast Deposition: Lesion Detection is a Safety Issue Too

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Disclosures: I have served as a consultant and speaker for several contrast manufacturers including GE Healthcare, Guerbet, and Bracco, and am currently conducting a retrospective trial with support from Bracco.

The tolerance of risk and the balanced appreciation of benefits associated with risks is fundamental to all medical interventions. To the extent that safety is the freedom from risk or danger, as has been pointed out by Dr. Emanuel Kanal, the missed diagnosis by not detecting pathology otherwise visible is not merely a decrease in efficacy, it is a safety issue. The scientific literature and the lay press have devoted much attention to the increased awareness of unintended gadolinium deposition in tissues after the administration of gadolinium based contrast agents (GBCAs) used to improve diagnosis in MR. The concerns are driven by the iatrogenic disease of nephrogenic systemic fibrosis (NSF). While appropriate caution is warranted for those with renal insufficiency, the benefits of contrast administration are often neglected in the current discussion and some historical perspective is helpful in guiding future practice. While not intended to be a comprehensive review, some relevant references are included.

The deposition of gadolinium in tissues has been described in animal models since at least 1984. (Huckle, Altun, Jay, & Semelka, 2016) The earliest report in humans was in 1989 (Tien, Brasch, Jackson, & Dillon, 1989) shortly after the introduction of Magnevist. The next report of gadolinium retention in humans was not until 1998, and the widespread awareness of NSF in 2006 and the reclassification of GBCAs into those more frequently associated with the NSF (ACR Manual on Contrast Media. V10.3. page 90). NSF prompted appropriate renal function screening prior to GBCA administration, and while such screening measures have effectively relegated NSF to an historic phenomenon, we do appreciate the lessons the entity provided. The concerns regarding the observation of tissue retention in the human brain raised by Kanda in 2014 sparked renewed concerns (Kanda, Ishii, Kawaguchi, Kitajima, & Takenaka, 2014) and many other investigators have published findings implicating all contrast agents in their capacity to contribute to brain deposition of gadolinium.

The current edition of the ACR Manual on Contrast Media (V10.3. pages 78-79) includes the May 2016 ACR-ASNR position statement on the use of gadolinium contrast agents. The gadolinium deposition in the brain may be dose dependent and can occur in patients with no clinical evidence of kidney or liver disease. To date, despite extensive review and attention, there have been no report of histologic changes of neurotoxicity, even among GBCAs with the highest rates of deposition. No clinical disease or entity has been linked to the retention of gadolinium in tissues. The position statement does advocate for additional research “to elucidate the mechanisms of deposition, the chelation state of these deposits, the relationship to GBCA stability and binding affinity, and theoretical toxic potential, which may be different for different GBCAs.” They note that “until we fully understand the mechanisms involved and their clinical consequences, the safety and tissue deposition potential of all GBCAs must be carefully evaluated.”

More than 300 million doses of GBCAs have been administered worldwide. There have been less than 1000 cases of NSF, and no new cases since the implementation of screening guidelines. There is widespread acknowledgement that gadolinium deposition has occurred since its introduction into the practice of MR. What needs to be properly acknowledged in this debate, and what was highlighted by the joint position statement is that GBCAs provide vital information rendering diagnoses not otherwise possible. Timely intervention means the world to those with a solitary metastasis or in differentiation patients with solitary or multiple metastases. The balanced approach to contrast utilization is the key. We should only use contrast with the appropriate clinical indications in patients with the appropriate renal function. We should also use the most efficacious of agents for a given indication. By doing so we make a meaningful and safe contribution to the care and management of our patients. As noted in the ACR-ASNR statement, "If the decision for an individual patient is made to use a GBCA for an MRI study, multiple factors need to be considered when selecting a GBCA, including diagnostic efficacy, relaxivity, rate of adverse reactions, dosing/concentration, and propensity to deposit in more sensitive organs such as the brain."

Huckle, J. E., Altun, E., Jay, M., & Semelka, R. C. (2016). Gadolinium Deposition in Humans: When Did We Learn That Gadolinium Was Deposited In Vivo? *Investigative Radiology*, *51*(4), 236–240. http://doi.org/10.1097/RLI.0000000000000228

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