Safety Aspects of Gadolinium Based Contrast Agents: Time to revisit practice?

Gadolinium chelates have been in diagnostic imaging arena for last 35 years. The sentinel reason for using gadolinium ion as an MR agent is because it has seven unpaired electrons and it shortens spin-lattice relaxation time (T1) of voxels in which they are present and this gives brighter signals to T1 weighted images. These linear gadolinium contrast agents include gadodiamide, gadoversetamide, gadopentetate dimeglumine, and gadobenate dimeglumine while the macrocyclic contrast agents include gadoteric acid and gadoteridol. Gadolinium based contrast agents (GBCA) are well tolerated by the patients, however, they are not absolutely hazards frees. Based on accumulated evidence based data, the side effects of GBCA hasa wide spectrum from simple allergic reactions to morbid or fatal nephrogenic systemic fibrosis (NSF).

The overall incidence of all acute adverse reactions ranges from 0.07%-2.4% and majority of these reactions are mild like itching, rash, nausea, headache and paresthesias. However, life-threatening anaphylactoid reactions are exceedingly rare with a reported incidence of 0.001% to 0.01%. Patients with prior history of reaction to GBCA are 8 times prone to have reaction during subsequent exposure which can be worse than the first episode. In such scenarios it is prudent to be cautious and a premedication protocol as recommended for iodinated CT contrast should be adopted. Incidence of extravasation for GBCA is 0.05% and injury caused by such extravasation is extremely low. However, hypertonic GBCA agents like gadopentatedimegluminеare more likely to cause symptomatic extravasation than nonionic GBCAs.

Some GBCAs like gadoversetamide and gadodiamide are likely to interfere with measurement of serum calcium resulting in falsely low serum calcium level. Early research data reveal a perpendicular alignment in magnetic field of deoxygenated RBCs with sickle cell deformity and based on this fact it was hypothesized that GBCA would enhance this effect with potential in-vivo vaso-occlusive or hemolytic complications. However, there is no reported evidence of such complications after GBCA in patients with sickle cell disease.

Nephrogenic systemic fibrosis (NSF) is a well-documented complication of GBCA in patients with advanced chronic kidney disease, with an acute kidney injury and substantial renal insufficiency. The risk of NSFdeveloping in these patients is particularly great when GBCAs are used in high doses such as when magnetic resonance angiography (MRA) is performed. However, with strict selection criteria based on basal renal function, there has been an exponential decline in incidence of NSF in patients undergoing GBCA MRI.

In recent years a cumulative data has shown remnant GBCA in the body long after it is injected even in patients with normal function. Most of the studies have focused upon retention of GBCA in brain resulting in higher intensity of dentate nucleus and globuspallidus on non-contrast T1WI. Based on previous data, high signal intensity in the dentate nucleus is linked with history of brain irradiation or multiple sclerosis, while high signal intensity of the globuspallidus has been linked to a number of conditions, including hepatic dysfunction, calcification, and neurofibromatosis.Recent observation also shows that magnitude of high signal on non-enhanced T1WI has a linear correlation with number of GBCA administrations.

However, so far there is no published study which speaks about the potential toxic effect of retained GBCA and this obviously is an area of robust research. Till we don't get the answer of this important safety aspect of GBCA upon human health, it is the time to revisit the current practice and selection criteria for administering GBCA. On the same note, the pharmaceutical industry must also strive to find a better and safer contrast for MRI suites.

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