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Symptoms Associated with Gadolinium Exposure (SAGE): A Suggested Term

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In this article, members of the American College of Radiology Committee on Drugs and Contrast Media propose a new term for symptoms reported after intravascular exposure to gadolinium-based contrast agents—Symptoms Associated with Gadolinium Exposure, or SAGE. This term is advocated in lieu of other proposed nomenclature that presumes a causal relationship that has not yet been scientifically verified. The purpose of this new term, SAGE, is to assist researchers and clinical providers in describing such symptoms without prematurely causally attributing them to a disease and to standardize reporting of these symptoms to allow for coherent interpretation of related studies.

Since their approval by the U.S. Food and Drug Administration (FDA) in 1988, gadolinium-based contrast agents (GBCAs) have revolutionized MRI, improving identification and characterization of diseases compared with unenhanced MRI and other imaging modalities. In general, GBCAs are safe with an extremely favorable risk-benefit profile. Known clinical risks include hypersensitivity reactions (approximately 1 in 1000 administrations, most of which are mild), generally benign physiologic reactions, and nephrogenic systemic fibrosis (NSF) in patients with severe kidney disease, usually after administration of one of three GBCAs considered the highest risk for patients with NSF and that are no longer used in many countries. These agents include gadodiamide (Omniscan, GE Healthcare), gadoversetamide (Optimark, Guerbet), and gadopentetate dimeglumine (Magnevist, Bayer Healthcare). In 2014, it was discovered that in addition to these risks, a small fraction of gadolinium in intravenously administered GBCAs is retained in a dose-dependent manner for months or years within neural and other human tissues, including in patients with normal kidney function (1–4). The extent of tissue retention parallels the kinetic lability of each GBCA, with less tissue retention associated with macrocyclic GBCA administration when compared with linear GBCAs (3–7). This retention has raised concerns among regulatory agencies, health care providers, and patients over the potential toxicity of this retention (5,6). Although no standard yet exists, we propose to define gadolinium retention as gadolinium, in any chemical form, remaining in tissues for 1 week or more after GBCA exposure, based on published elimination half-lives in humans (ie, 1.5 hours with normal kidney function, 8 hours with moderate kidney impairment, and 32 hours with severe kidney impairment), and the expectation of steady-state conditions after five half-lives (8).

The acute tolerance and toxicities of various chemical forms of gadolinium, including free elemental and chelated forms, are well known and have been extensively studied (9,10). Much of the toxicity of elemental gadolinium is derived from its position in the periodic table in the middle of the lanthanide series of rare earth metals. Gadolinium has an ionic radius of 0.94 Å, a value that is nearly identical to elemental calcium, 0.99 Å (10). As such, it is capable of competing with calcium in myriad biophysical processes, including interaction and interference with calcium-dependent cellular and biochemical pathways within the reticuloendothelial system, calcium-dependent enzymatic reactions, ion channel function, and cellular phagocytosis. However, as gadolinium is a trivalent cation in its normal oxidation state, it binds to and interacts with relevant biomolecules with a much higher affinity than does the divalent calcium atom (10). Such interaction may adversely alter the enzyme kinetics of affected biologic processes, resulting in disruption of cellular homeostasis, cellular dysfunction, and injury.

Fortunately, the chelation of gadolinium with organic polyamine carboxylates to form GBCAs, in either linear or macrocyclic form, has profound effects on the biologic toxicity and activity of gadolinium. Chelation fundamentally changes the biodistribution and bioavailability of gadolinium, limiting its ability to interact with biomolecules and to interfere with calcium-dependent processes (6,9,10). In contradistinction to "free" gadolinium (ie, unchelated gadolinium that is able to interact with nearby molecules), where median lethal dose, or LD50, values of 0.1 to 0.2 mmol/kg are common (LD50 is the dose sufficient to kill 50% of patients exposed), LD50 values of gadolinium chelate GBCAs are much higher, ranging from 6 mmol/kg to more than 30 mmol/kg (6,11,12). Thus, the chelation of gadolinium in a GBCA decreases the acute toxicity dose threshold by several orders of magnitude. The standard human clinical dose of 0.1 mmol/kg would be highly toxic or lethal if one were administering free forms of gadolinium, whereas this dose is well within the acceptable thresholds of safety when complexed as a GBCA.

Long-term retention of chemical forms of gadolinium within the tissues of patients with normal kidney function highlights the complex and incompletely understood

Abbreviations

FDA = U.S. Food and Drug Administration, GBCA = gadolinium-based contrast agent, NSF = nephrogenic systemic fibrosis

Summary

The American College of Radiology Committee on Drugs and Contrast Media proposes new nomenclature for Symptoms Associated with Gadolinium Exposure, or SAGE. The purpose is to assist researchers and clinical providers in describing such symptoms without prematurely attributing them to a disease and to standardize reporting to allow for coherent interpretation of related studies.

Essentials

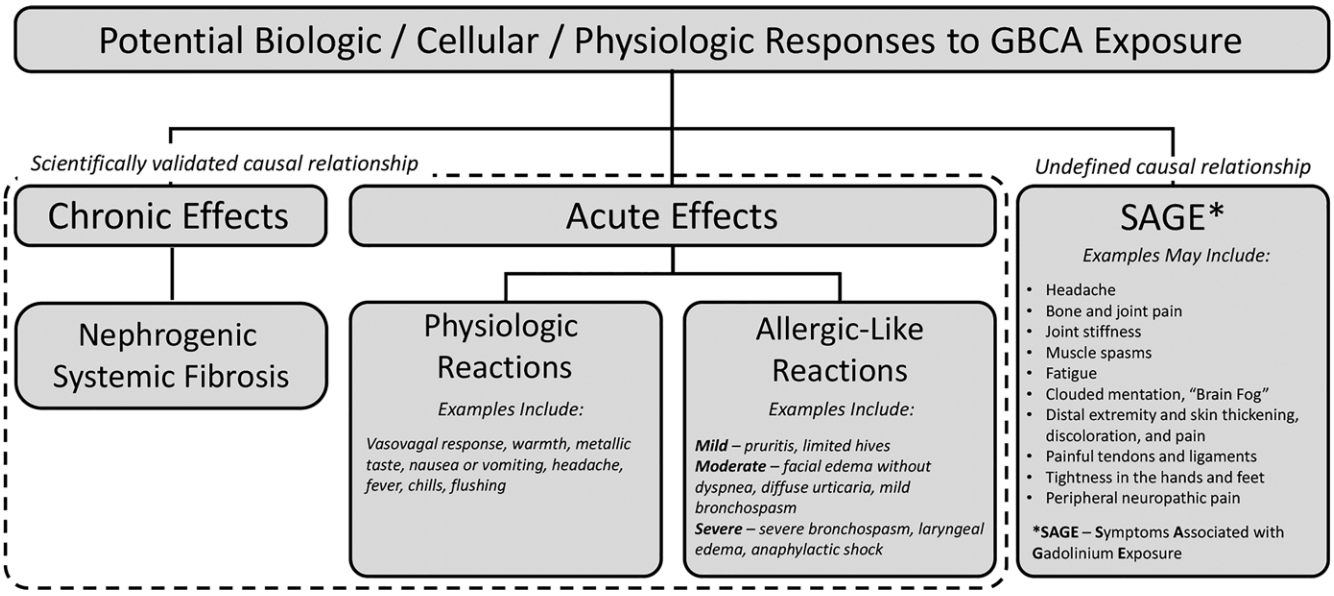
- Symptoms Associated with Gadolinium Exposure, or SAGE, is a new term endorsed by the American College of Radiology; it refers to symptoms following gadolinium-based contrast agent (GBCA) administration that are unrelated to established early-onset (ie, acute hypersensitivity and physiologic reactions) and late-onset (ie, nephrogenic systemic fibrosis) adverse effects from GBCAs.
- SAGE is stratified into early-onset (<24 hours after GBCA exposure) and late-onset (≥24 hours after GBCA exposure) cohorts.
- SAGE is intended to be used when a causal relationship between GBCA and symptoms is unknown (eg, nonspecific symptoms associated with gadolinium retention).

biodistribution of these agents. It was historically assumed that in patients without severe kidney disease, all intravenously administered gadolinium would be excreted within a short period of time as an intact chelate (6). This assumption was central to the presumed safety of these chelates. Chelate dissociation could release free gadolinium (13). At the time of FDA approval, chelate dissociation was thought to occur on a much slower timescale of weeks to years than physiologic clearance of hours to days (14). It has subsequently been shown that only macrocyclic GBCAs possess sufficient kinetic inertness in vivo to remain stable as an intact chelate over the entire time frame of expected physiologic clearance (14,15). The identification of various retained chemical forms of gadolinium within human tissues, particularly following linear GBCA exposure, challenges this assumption and highlights the gap between the predicted and observed stability of GBCAs, suggesting that GBCAs experience a wide range of chemical environments in vivo that may adversely affect their lability (15,16).

Although efforts are still ongoing to elucidate the exact chemical identities of these retained forms of gadolinium, their toxic potential can be projected with reasonable certainty. Current estimates suggest that between 0.1% and 1%, depending on GBCA chemical identity and renal clearance, of the administered gadolinium is retained approximately 1 week after a single 0.1 mmol/kg dose of a typical GBCA (6,17). As our understanding of the dynamic biodistribution and clearance of these chemical species remains relatively undefined, particularly in humans, this 1-week time frame is still somewhat arbitrary. This means that at approximately 1 week after exposure, between 1:1000 and 1:100 of the original dose, or 0.1 to 1 μmol/kg, is retained in total across all affected tissues. Therefore, even if dozens of cumulative doses are administered—and even if all retained gadolinium was in the most toxic, free, elemental form—the amount of retained gadolinium would still be several orders of magnitude below well-established toxicity thresholds. For example, it has been shown that approximately 0.0001% of the original injected dose of gadodiamide is retained in whole-brain parenchyma, with specific neuroanatomic regions (eg, cortex) experiencing even lower effective doses (6,17). Because much of this gadolinium has been shown to be sequestered in specific tissue reservoirs, the effective amount of "free circulating gadolinium" capable of toxic interference with calcium-dependent processes is likely several orders of magnitude lower than these estimates of retention (3,6,9,10).

In parallel with chemical, pharmacologic, and toxicologic studies, histopathologic examinations of postmortem tissues among patients exposed to high cumulative doses of GBCA have not revealed compelling evidence of tissue or organ toxicity, even among organs exposed to relatively higher doses (eg, organs of excretion, such as the kidneys, and, for some GBCAs, the liver) or those thought to be particularly susceptible to injury (eg, the brain) (6). However, recent animal model studies have questioned whether there may be subtle tissue toxicity from GBCA exposure. Radbruch et al (18) recently showed that mice exposed to linear GBCAs had lower intraepidermal nerve fiber densities when compared with mice exposed to macrocyclic GBCAs, and postulated these effects may account for the peripheral nerve symptoms (eg, burning sensation) reported by some patients after GBCA administration. Efforts have been underway to determine the clinical significance of retained gadolinium in human tissues. Fortunately, the preponderance of evidence suggests that at normal clinical doses, even when patients are subjected to large cumulative doses of GBCA over time, no scientifically validated adverse clinical effects have been observed in controlled data sets (6). Additionally, it appears that a majority of retained gadolinium, even after apparently undergoing dechelation, either reassociates with the ligand or forms biologically inactive chemical forms through precipitation or association with other cellular polyanionic structures (6,15,17).

Notwithstanding the absence of data in properly controlled studies to suggest toxicity from retained gadolinium in tissues, some have suggested a causal association between gadolinium retention after GBCA administration and a spectrum of symptoms reported by a very small minority of patients (<150 patients) (19–21). The spectrum of reported symptoms and signs includes neurologic, cognitive, musculoskeletal, and other nonspecific complaints, as well as a potential elevation in cytokine levels (22), and has been given a variety of names including gadolinium deposition disease, gadolinium storage disease, and gadolinium storage condition (18). Although some have proposed a delayed immunologic reaction to gadolinium as the mechanism of these diverse symptoms, to date there is no scientific evidence in support of this mechanism (19). The timing of these associations has been reported to vary from minutes to months after GBCA exposure (19–21). In addition to the incongruent timing, these symptoms have been reported after exposure to both linear and macrocyclic GBCAs. The frequency of these reports does not appear to correlate with GBCA subclass nor the relative amounts of retained gadolinium that have been measured in postmortem human or animal tissues (23,24). Such reports are difficult to reconcile and attribute to gadolinium retention because it is now well known that macrocyclic GBCA exposure is associated with markedly lower (and in some cases, undetectable) levels of retained gadolinium when compared with linear GBCA exposure and that much



Flowchart of proposed term for Symptoms Associated with Gadolinium Exposure, or SAGE, and its relationship to established diseases or conditions caused by gadolinium-based contrast agents (GBCAs).

of the transiently retained gadolinium after macrocyclic GBCA exposure is likely in the form of an intact chelate rather than a dechelated chemical form of gadolinium that is thought to result from linear GBCA exposure (6,15).

Despite the lack of compelling evidence of a causal association between GBCA exposure and the onset of these diverse symptoms, clinics have been established to treat individuals for presumed gadolinium toxicity through chelation therapy—a therapy that was shown to be of questionable safety and efficacy when it was used for the treatment of NSF (25). The American College of Radiology Committee on Drugs and Contrast Media feels that a disease-specific term is inappropriate at this time because it presumes a causal association that has not been proven through scientific investigation. Furthermore, treatment of a constellation of disparate symptoms without a clear mechanism and that have not been confirmed to be a disease puts patients at unnecessary risk. Risk can result from the cochelation of essential serum cations and the re-equilibration of retained gadolinium species with larger tissue reservoirs during chelation.

The existence of a new (non-NSF) named disease for patients with symptoms attributed to long-term gadolinium retention remains highly controversial for several reasons. First, there is no credible disease mechanism to encompass all reported symptoms (5,6,23). Second, the timing of symptom onset is inconsistent, and, for those patients in whom the onset occurs minutes after GBCA administration, there is insufficient time for the GBCA to reach equilibrium, meaningfully de-chelate, or be retained within tissue (6–10). Third, many self-reported symptoms are nonspecific and are present in nearly all phase III clinical trials of prescribed agents, drugs, and placebos before FDA authorization (6). Fourth, some of these self-reported symptoms are present to a lesser extent before GBCA exposure. In existing reports, it is not always clear which symptoms or signs were present before GBCA administration, including those that may have prompted the order for the MRI examination. For these reasons, it remains possible that because imaging is often performed at the inflection point in a patient's manifestation of symptoms, associated symptoms may be a diagnosis of misattribution and may be unrelated to GBCA exposure.

In 2017, the FDA evaluated the existing data and found no scientific evidence to suggest a causal association between GBCA exposure and the development of symptoms in patients with normal kidney function (21). Undeterred, several patients brought legal action against GBCA manufacturers seeking damages for these symptoms (26–28). However, as of this writing, nearly all litigation has ceased, with a majority of cases having been withdrawn by plaintiffs. After the ruling in *Davis v McKesson Corp* on October 25, 2019, the ninth district court in Arizona affirmed the findings of the FDA insofar as it ruled that no compelling evidence between GBCA exposure and non-NSF disease exists (26). It further denied the motion by the plaintiffs to enjoin existing cases into multidistrict litigation, effectively preventing future class-action litigation. This district court ruled that a majority of the expert witness testimony provided by the plaintiffs was invalid because it was in conflict with statements made by the same expert witnesses in other legal and scientific meetings, including testimony provided at the 2017 FDA Medical Imaging Drugs Advisory Committee meeting (21).

Despite the absence of scientific data indicating harm from gadolinium retention, there is the potential for unmeasured rare or subtle toxic effects, for example, the recent potential findings of Radbruch et al (18). Because of evidence of gadolinium accumulation in central nervous system tissues, the FDA required that the four GBCA manufacturers—Bayer Healthcare, Bracco Diagnostics, GE Healthcare, and Guerbet—participate in a longitudinal multicenter prospective trial (ClinicalTrials.gov identifier: NCT04373564; Effect on Body Movement and Mental Skills in Patients Who Received Gadolinium-based Contrast Media for MR Examination Multiple Times within 5 Years, or ODYSSEY trial) designed to detect neurologic and other symptoms associated with gadolinium exposure. While neither exhaustive in scope nor study duration, efforts are currently

underway for this trial and it may, in due time, provide reasonably compelling evidence to affirm or dispute whether gadolinium retention causes harm. Similarly, although the National Institutes of Health, American College of Radiology, and RSNA do not recognize a disease associated with gadolinium retention, they support the need for further study.

To assist such efforts, the American College of Radiology Committee on Drugs and Contrast Media proposes and endorses the following term for Symptoms Associated with Gadolinium Exposure—SAGE. This term is intended to replace *gadolinium deposition disease, gadolinium storage disease, gadolinium storage condition*, and other nomenclature that prematurely presumes a causal relationship between gadolinium retention and the manifestations of myriad symptoms described earlier (Figure). This term refers to those symptoms unrelated to established early-onset (ie, acute hypersensitivity and physiologic reactions) and late-onset (ie, NSF in patients with severe kidney disease) adverse effects from GBCA exposure, and which may occur irrespective of kidney function. To differentiate early-onset versus late-onset physiochemical processes, SAGE should be stratified into early-onset (<24 hours after GBCA exposure) and late-onset (≥24 hours after GBCA exposure) cohorts. This proposal is designed to enable researchers and clinical providers to describe symptoms temporally associated with gadolinium exposure without necessarily causally attributing them to a disease. This is because any hypothetical disease would be based mostly on conjecture at this time and would not be generally recognized by the medical community because a causal association has not yet been proven through scientific investigation. It is hoped this proposed nomenclature will better articulate the current state of knowledge (ie, enabling discussion without premature disease attribution) and will improve communication in related research. Such a term provides the opportunity for further refinement should future evidence surface that compels the FDA, American College of Radiology, and other entities to re-evaluate the potential causal association between long-term gadolinium retention and symptoms. However, at this time, current scientific and clinical data suggest a coincidental rather than causal relationship.

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