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Gadolinium-based contrast agents: A review of recent safety concerns and current Australia and New Zealand recommendations

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Abstract
Introduction: Gadolinium-based contrast agents (GBCAs) are widely used in magnetic resonance imaging (MRI) to enhance visualization of vascular structures and pathological lesions, thereby improving diagnostic accuracy. While generally safe, their increasing use has raised concerns regarding adverse effects, particularly nephrogenic systemic fibrosis (NSF) in patients with renal impairment, and tissue retention of gadolinium even in individuals with normal renal function. This review aims to critically examine the current safety profile of GBCAs, including known toxicities, deposition risks, and professional guidelines for clinical use.
Methods: A narrative literature review was conducted, focusing on peer-reviewed studies, clinical trials, and professional society guidelines published between 1988 and 2025. Emphasis was placed on evidence surrounding GBCA classification (linear vs. macrocyclic), toxicological mechanisms, risk of NSF, gadolinium deposition disease (GDD), potential nephrotoxicity, and recent recommendations.
Results: Linear GBCAs demonstrate a higher risk of transmetalation and gadolinium retention compared to macrocyclic agents. NSF, although rare, occurs more frequently in patients with severe renal impairment exposed to linear agents. GDD remains a controversial and poorly understood phenomen on, with no definitive histopathological correlates. Evidence linking GBCAs to nephrotoxicity is limited and largely inconclusive. Current guidelines recommend cautious use of GBCAs in high-risk populations, preference for macrocyclic agents, minimisation of contrast dose, and consideration of post-procedural dialysis in selected cases.
Conclusion: Although GBCAs are indispensable in modern diagnostic imaging, their use is not without risks. Understanding the differential safety profiles of contrast agents, especially in vulnerable populations, is essential. Macrocyclic GBCAs are generally safer and preferred in high-risk patients. Strict adherence to updated clinical guidelines and ongoing pharmacovigilance is critical to balancing diagnostic benefits with patient safety.

Keywords: Gadolinium-based contrast agents (GBCAs), MRI, nephrogenic systemic fibrosis (NSF), gadolinium deposition disease (GDD), nephrotoxicity, linear GBCAs, macrocyclic GBCAs

Introduction

Magnetic resonance imaging (MRI) is a non-invasive diagnostic imaging tool widely utilised across medical specialties to assess a variety of diseases. It offers high-resolution, soft tissue contrast without ionising radiation, making it a valuable imaging modality across a wide range of specialties. In many cases, gadolinium-based contrast agents (GBCAs) are utilised to enhance the visibility of vascular structures and pathological lesions. GBCAs can significantly improve diagnostic accuracy in specific settings such as malignant tumours and inflammatory diseases. While generally considered safe in most circumstances, their increasing use globally has recently made their associated toxicity more apparent. GBCAs have been linked to nephrogenic systemic fibrosis (NSF) in patients with renal impairment, and more recently, tissue retention of gadolinium has raised concerns even among patients with normal kidney function. As the use of GBCAs continues to rise globally, understanding of their safety profile is essential. This review article aims to examine the current evidence on GBCA safety, adverse effects, tissue retention, and existing guidelines regarding their administration.

History

Soon after the discovery of MRI, the use of paramagnetic ions was proposed to increase contrast due to their susceptibility to external magnetic fields. This property is attributed to their unpaired electrons. Multiple compounds were proposed, including manganese, chromium, and copper, but gadolinium showed the most promise [1]. However, gadolinium ions are highly toxic and needed to be chelated to prevent interaction with surrounding proteins and tissue, facilitate elimination, and reduce accumulation. Their toxic effects are believed to be due to free gadolinium ions interfering with calcium ion channels, resulting in neurotransmitter inhibition, muscle contraction disruption, and mitochondrial dysfunction [2].

Gadolinium-based contrast agents utilise gadolinium ions combined with specific chelating agents. The first GBCA approved for use was Magnevist (gadopentate) in 1988, which consists of a gadolinium ion chelated in diethylenetriamine penta-acetic acid (DTPA) [3]. Since then, multiple other GBCAs have been developed, each with unique chelating agents and pharmacokinetic characteristics. GBCAs are generally categorised as either linear or macrocyclic based on the structure of their chelating agent. Linear agents have a chain-like structure that binds to gadolinium, whereas macrocyclic agents have a closed, ring-like structure that functions as a cage [4]. While both types demonstrate strong binding of their gadolinium ion under physiological conditions, macrocyclic GBCAs are deemed more stable and less likely to undergo transmetalation - a process where the gadolinium ion is replaced by another ion such as calcium, leading to its release [1]. Transmetalation has been suggested as a potential cause for nephrogenic systemic fibrosis and nephrotoxicity, which are discussed in more detail below.

Nephrogenic Systemic Fibrosis

The first case of a new fibrosing dermopathy distinct from scleroderma was reported in 1997. This condition, named nephrogenic systemic fibrosis, causes cutaneous thickening with indurated and discoloured skin that primarily affects the limbs and trunk, sparing the face [5]. More serious disease can affect subdermal muscle and tendons. Although rare overall, cases that involve fibrosis of internal organs such as the pericardium and dura mater have been described, and it is associated with high morbidity and mortality [5]. Since its first recognition, hundreds of cases have been reported, varying in severity, time of onset, and GBCA dose exposure.

It was not until 2007 that Collidge *et al* [6]. suggested a link between NSF and GBCA exposure among patients with renal impairment [6]. In most of the cases he reviewed, patients had been administered linear agents such as gadodiamide and a positive correlation was found between cumulative GBCA dose and NSF risk. This was particularly strong among patients with severe or acute renal failure. NSF typically presents within weeks to months after initial GBCA administration, though delayed cases in the range of years have also been described [7]. Symptoms typically begin as pruritic, erythematous patches accompanied by pain and oedema. This can often progress to joint stiffness, muscle weakness, and deep bone pain. Diagnosis is based on skin biopsy showing thickened dermal collagen, increased CD34+ spindle cells, and dermal mucin [8]. Although the pathogenesis of NSF remains poorly understood, it is believed to involve prolonged GBCA retention due to renal impairment, increasing the likelihood of transmetalation with release of free gadolinium ions. Other proposed risk factors include presence systemic inflammation and infection, while other studies suggest that the chelating agent itself may stimulate fibrosis, independent of free gadolinium ions [9]. A definitive mechanism has yet to be established.

Although linear GBCAs are more prone to transmetalation, the overall risk of NSF from either GBCA class remains low. Woolen *et al*. estimated the risk of NSF among stage 4 and 5 chronic kidney disease (CKD) patients who received macrocyclic GBCAs to be less than 0.07% [11]. Nevertheless, the recent identification of this link has led to stricter use of GBCAs, especially in patients with an estimated glomerular filtration rate (eGFR) below 30 ml/min/1.73 m [2]. Royal Australia New Zealand College of Radiology (RANZCR) has estimated the risk of NSF to be approximately 1% for CKD stage 5 patients receiving a single dose of linear agents such as Magnevist (gadopentetate) or Omniscan (gadodiamide) [10]. Macrocyclic GBCAs, such as Gadovist (gadobutrol), present a lower overall risk in comparison. It is important to emphasise that there is likely no absolute eGFR threshold for NSF risk, although higher eGFR generally indicates lower overall risk of developing NSF. Dialysis has been considered as a potential mitigation strategy due to the role of renal failure in NSF development. However, there is currently no proven method to prevent or treat NSF [12]. Despite ongoing uncertainties, NSF is recognised as a rare, multifactorial condition influenced by cumulative GBCA dose and renal function.

Gadolinium Deposition Disease

Gadolinium deposition disease was found after unexpected high signal intensities in the dentate nucleus and globus pallidus on non-enhanced T1-weighted MRIs were first noted in 2014 by Kanda *et al* [13]. This retrospective study identified a correlation between signal intensity in these regions and prior GBCA exposure, independent of renal function. Similar findings were later confirmed in multiple sclerosis and meningioma patients who frequently undergo GBCA-enhanced MRIs [15]. Further studies on these patients have shown that the degree of gadolinium retention is 2- to 4-fold higher in patients exposed to linear vs macrocyclic GBCAs. Given its relatively recent discovery of GDD, quality prospective clinical trials are lacking.

Symptoms of GDD are largely non-specific including fatigue and mental confusion, most of which are mild and self-resolve within 24 hours [16]. A 2019 study by Parillo *et al*. involving over 1,000 patients found that there is a 2-fold increase in symptoms of GDD among patient who received GBCA-enhanced MRIs compared to those who received non-enhanced MRIs [17]. On further inspection, no demonstratable histological changes to tissues laden with gadolinium were found on post-mortem biopsies that can contribute to disease [2]. It is also important to note that many preclinical studies using high and repeated GBCA doses have not shown toxic effects. Given the widespread use of GBCAs, the incidence of GDD remains negligible [18]. Despite these recent findings, the European Medicines Agency has withdrawn linear GBCAs from the market in 2017 [1]. On the other hand, the US FDA and Australian TGA have not followed suit. RANZCR recommends using

macrocyclic agents when appropriate, especially in patients with renal impairment, to minimise gadolinium retention [10].

Nephrotoxicity

Evidence linking GBCAs to nephrotoxicity is limited. Following intravenous administration, GBCAs distribute rapidly into interstitial compartments, with only liver-specific agents such as Primovist (gadoxetate) thought to enter cells [1]. Clearance of GBCAs is primarily through glomerular filtration within the kidney with liver-specific agents being partially cleared by the liver as well [10]. In individuals with normal renal function, around 90% of GBCAs are excreted unchanged in the urine within 24 hours [22]. Limited data are available beyond this period, but the presence of gadolinium in urine long after administration suggests tissue retention and subsequent gradual release. In patients with reduced glomerular filtration, GBCA retention in circulation can be up to 12 times higher than normal [18].

Some favour GBCAs over iodinated contrast agents, hypothesising a lower risk of contrast-induced nephropathy (CIN) due to their lower viscosity and relative dose [19]. However, there is a lack of evidence for either side of this argument. Naito *et al*. observed a higher risk of CIN in CKD stage 1-2 patients administered gadodiamide compared to those given gadopentetate (both linear agents), in a study of nearly 700 patients [20]. However, this study had significant limitations, such as CKD classification based on a single blood test and lack of adjustment for confounding factors including cardiac failure and nephrotoxic medication use. Laboratory studies have also reported accumulation of lipid-laden vacuoles in renal proximal tubules following GBCA exposure [21]. While gadolinium was found within these vacuoles, the biological effects are unknown. This finding also challenges the previous held assumption that GBCAs remain confined to the extracellular space.

Current RANZCR Recommendations

Although GBCA-related diseases have only recently been identified, their prevalence remains low given the vast number of contrast-enhanced MRIs performed annually worldwide. Nonetheless, caution is warranted. Clinically, GBCAs should only be administered when medically justified, and alternative imaging modalities such as unenhanced MRI, CT, or ultrasound are deemed inappropriate. All contrast-enhanced MRIs should include clear documentation of the type and dose of GBCA used.

RANZCR identifies high-risk groups as those with eGFR less than 30 ml/min/1.73 m [2] and patients on haemodialysis or peritoneal dialysis [10]. This group also includes pregnant women, neonates, and infants under one year of age regardless of their renal function. In these high-risk patients, guidelines recommend using the lowest possible GBCA dose (0.1 mmol/kg) and avoiding repeated scans. Patients with severe renal disease should be evaluated for post-contrast haemodialysis when appropriate by the renal team. Behave *et al* suggests that one session can remove approximately 75% of circulating gadolinium [23]. For patients already on haemodialysis, MRIs should be scheduled just prior to their regular session, with consideration for an additional session the following day. Peritoneal dialysis patients have the highest risk for NSF and GBCA should only be given when necessary. Kallen *et al*. suggests that they are up to 7-times more likely to develop NSF than patients on haemodialysis [24]. Post GBCA-enhancement MRI for these patients should be followed up with frequent peritoneal dialysis for at least 48-hours and consideration for haemodialysis.

GBCAs with the lowest theoretical toxicity, such as macrocyclic agents, should be recommended over linear agents for high-risk patients. Furthermore, intravenous iron transfusions should also be avoided prior to GBCA administration to reduce risk of transmetalation [25]. All high-risk patients must be fully informed about the potential risks and benefits of GBCA use with written consent obtained prior. Any suspected cases of NSF in Australia should also be reported to the Therapeutic Goods Administration and the GBCA manufacturer.

Conclusion

GBCAs have revolutionised the diagnostic power of MRI, particularly in oncology, neurology, and cardiovascular imaging. However, as knowledge of their safety profile evolves, so too must clinical practice. GBCAs are associated with rare but serious conditions such as NSF and may lead to gadolinium retention in patients with and without renal impairment. While macrocyclic GBCAs are considered safer, no agent is entirely risk-free. Clinicians must carefully evaluate the necessity of contrast administration on a case-by-case basis, especially in vulnerable populations including those with renal dysfunction, infants, and pregnant women. Continued vigilance, adherence to up-to-date guidelines, and research into safer contrast agents remain essential to ensure patient safety.

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