

REVIEW

Side Effects and Complications of Magnetic Resonance Contrast Media

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ABBREVIATIONS

CT = computed tomography
DM = diabetes mellitus
eGFR = estimated glomerular filtration rate
GFR = glomerular filtration rate
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
NSF = nephrogenic systemic fibrosis

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ABSTRACT

Contrast media used in radiology are iodine based for computed tomography (CT) examinations and gadolinium based for magnetic resonance imaging (MRI) examinations. Initially, gadolinium based contrast media were thought to be safe and non-nephrotoxic. Later on, several studies revealed that they can also be nephrotoxic at increased doses. Additionally, another complication from their use is systematic nephrogenic fibrosis. Gadolinium based contrast media can be safe in healthy and renal insufficiency patients if used at specific doses. These complications are herein briefly reviewed and guidelines and techniques for their avoidance are discussed.

INTRODUCTION

The development of radiologic contrast media originated with the use of iodinated contrast media in radiography in 1918. A number of ionic high osmolar contrast media was synthesized through the 1950s and 1960s. Later, non-ionic low-osmolar contrast media were synthesized to minimize the incidence of immediate type hypersensitivity reactions to high osmolar contrast media. The incidence of these reactions was further lowered by iso-osmolar contrast media.¹ The use of iodinated contrast media has been increased due to the increased use of radiologic diagnostic modalities and interventional angiographic procedures. However, the occurrence of acute renal failure, known as contrast media induced nephropathy, is still a major complication. According to the guidelines of the Contrast Media Safety Committee of the European Society of Urogenital Radiology, contrast media nephrotoxicity is defined as an increase in serum creatinine level of 0.5 mg/dl (44 µmol/l) or more or 25% or greater above the baseline value occurring within 3 days after intravascular contrast administration without an alternative cause.²

Contrast induced nephropathy has become the third leading cause of acute renal failure necessitating hospitalization.³ The overall incidence has been reported between 1-2%^{3,4} in the general population and 11% in hospitalized patients.⁵ However, in patients with underlying hypertension, cardiovascular disease, diabetes mellitus or pre-existing renal insufficiency, the incidence is higher and may be as high as 20-50%.^{3,4,6} Other risk factors include an increased volume of contrast media use, repeated use within 72 hours, dehydration, advanced age (over 70 years), intake of concomitant nephrotoxic

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drugs, multiple myeloma and liver disease.¹ Another serious adverse reaction of contrast media is nephrogenic systemic fibrosis (NSF), which is a fibroproliferative disease confined to patients with advanced chronic kidney disease and patients with acute renal injury and substantial renal insufficiency. Other risk factors that may be associated include edema, systemic inflammation and recent surgery.

In 1988 the Food and Drug Administration of the USA approved gadolinium as a contrast agent to provide a clearer picture of organs and tissues in patients undergoing magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). Gadolinium-based contrast agents have been successfully employed to enhance MRI images by affecting T1 and T2 relaxation times, providing a stronger MRI signal and a brighter image. In order to reduce toxicity, only gadolinium chelated agents are used. Although initially thought to be non-nephrotoxic, conferring a significant advantage over the iodinated contrast agents used in X-ray procedures, gadolinium based agents have been shown to be nephrotoxic, particularly when used in higher dosages and especially in patients with chronic renal insufficiency. Furthermore, an association between gadolinium based contrast media exposure and NSF has also been observed and several risk factors have been identified.

CHARACTERISTICS OF GADOLINIUM CHELATES

Gadolinium (Gd) is a member of lanthanide series of transition metals. Its biochemical and physiochemical properties make it extremely useful as a contrast agent in MRI in order to enhance various body organs and tissues. There are many cases in which the use of gadolinium is essential such as in brain and spinal cord masses, demyelinating diseases, bone tumors and infection or rheumatologic diseases and study of abdominal or pelvic masses, etc. However, the free ionic form (Gd³⁺) is highly toxic and has been shown to precipitate in tissues and obstruct calcium ion passage through muscle and nerve cells.¹ To prevent the toxic effects it needs to be sequestered by nontoxic substances, a chelate such as macrocyclic molecules and linear molecules.⁷ These chelated agents demonstrate a 500-fold increase in renal excretion when compared with excretion of free gadolinium.^{8,9} In general, macrocyclic chelates such as gadoterate meglumine or gadoteridol are more stable than linear molecules. Non ionic preparations are less stable in comparison to ionic preparations (Table 1).¹⁰

PHARMACOKINETICS OF GADOLINIUM CHELATE

Gadolinium chelates reach rapid equilibrium between

TABLE 1. Gadolinium Chelates Available for Clinical Use

Chemical Compound	Type	Approved IV Dose (mmol/kg)
Gadopentetate dimegumine	Ionic linear	0.1-0.3
Gadoteridol	Nonionic cyclic	0.1-0.2
Gadoterate	Ionic cyclic	0.1-0.2
Gadodiamide	Nonionic linear	0.1-0.3
Gadobenate dimeglumine	Ionic linear	0.05-0.1
Gadoversetamide	Non ionic linear	0.1
Gadobutrol	Non ionic cyclic	0.1-0.3
Gadofosveset trisodium	Linear ionic	0.01-0.05

IV = intravenous

plasma and interstitial compartments. They do not undergo biologic transformation and are eliminated unchanged, almost exclusively by glomerular filtration, without any tubular secretion, with mean terminal half-life of 2 hours.¹ In patients with normal renal function, about 98% of gadolinium chelate is excreted within 24 hours in the urine with less than 3% being eliminated in the feces.¹¹ In patients with moderate (creatinine clearance 30-60 ml/min) or severe renal insufficiency (clearance 15-30 ml/min), gadolinium chelate elimination is markedly prolonged.¹

PROBABLE MECHANISM OF NEPHROTOXICITY OF CONTRAST MEDIA

The pathogenesis of contrast induced nephropathy by iodinated contrast media is thought to be due to hypoxic or ischemic injury to tubular cells and due to direct toxicity by generation of reactive oxygen species. Similar to iodinated contrast media, gadolinium chelates may result in nephrotoxicity via a direct cytotoxic effect on renal tubular cells. Accumulation of free Gd³⁺ has also been suggested as a causative factor of contrast induced nephropathy. In patients with normal renal function, the excretion of gadolinium complex is rapid and the concentration of the free Gd³⁺ is very low. On the contrary, in patients with reduced renal function there is an increase in the elimination half-life of gadolinium chelates, which results in accumulation of toxic free Gd³⁺.¹² Additionally, free Gd³⁺ can be released in the presence of high concentration of competing cations such as copper and zinc, called transmetallation, when gadolinium complexes remain in the body for a prolonged time¹³ as in patients with renal insufficiency.

RENAL SAFETY OF GADOLINIUM BASED CONTRAST MEDIA IN PATIENTS WITH NORMAL RENAL FUNCTION

There are plenty of studies dealing with renal safety in patients with normal renal function.¹⁴⁻¹⁷ In a retrospective study in which the effect of gadolinium chelates was examined in healthy individuals, it was observed that no one developed contrast induced nephropathy. The authors concluded that gadolinium-based agents are safe and well tolerated.¹⁸ In another retrospective study, serum creatinine levels were compared before and after both gadolinium and iodinated examinations were performed on separate days within a 6-month period. Creatinine levels did not increase in patients with normal renal function after gadolinium chelate injection, in contrast to patients who received iodinated contrast media in whom the incidence of contrast induced nephropathy was 2.6%.¹⁹ In another study, no significant difference in serum creatinine was observed in patients receiving a mean dose of gadolinium chelate of 0.14 mmol/kg in patients with normal renal function.²⁰ The reports of gadolinium chelates as contrast media in healthy individuals have been uniformly favorable in terms of their tolerance and effect on renal function with no reported cases of contrast agent induced nephropathy. Gadolinium chelates in healthy individuals are safe if used intravenously in doses of 0.1 mmol/kg.¹

RENAL TOXICITY OF GADOLINIUM IN PATIENTS WITH RENAL INSUFFICIENCY

Over the previous several years, gadolinium based contrast media had been considered safe and non-nephrotoxic as compared with iodinated ones. However, recent reports have questioned this assertion. In one study,²¹ the authors compared patients with a creatinine clearance rate <60 ml/min/1.73 m² who received prophylactic intravenous hydration and oral N-acetylcysteine and gadodiamide-iodine mixture or an iodinated contrast media alone during cardiac catheterization. Although less iodinated contrast media was used in the gadodiamide group, there was no difference in the incidence of contrast induced nephropathy between the two groups. The authors concluded that the incidence of contrast induced nephropathy was not decreased in high risk patients receiving a gadolinium-chelate-iodinated mixture rather than iodinated alone.

Case reports of acute renal failure after administering a gadolinium dose of 0.1-0.44 mmol/kg in patients with renal insufficiency have appeared in the literature.²²⁻²⁴ All patients had diabetes mellitus (DM) type 2 and/or hypertension. Renal biopsies suggested acute tubular necrosis. In another study, deterioration of renal function occurred after intra-arterial administration of a dose >0.2 mmol/kg in patients with renal insufficiency (creatinine clearance <60 ml/min/1.73 m²), which

is frequently associated with DM or hypertension.¹ Moreover, another study concluded that underlying renal insufficiency, DM and cardiovascular disease must be identified before the patient receives gadolinium chelate and doses should not be greater than 0.4 mmol/kg.²⁵ In another study,²⁶ no change in renal function occurred after injection of 0.1 mmol/kg of gadodiamide in patients with severely impaired renal function (glomerular filtration rate-GFR of 2-10 ml/min/1.73m²) and in patients undergoing hemodialysis or peritoneal dialysis. Gadodiamide injection was followed by 500 ml of saline administered intravenously during the first 3 hours. In this study, none of the patients who had diabetes or received drugs was suspected of having a nephrotoxic effect.

In a retrospective study,²⁷ it was suggested that gadolinium-based contrast media can induce acute kidney injury in patients with renal impairment with the usual dose for MRI examinations. After all other causes of acute kidney disease, such as severe heart failure and shock, were excluded, the authors observed a decrease in GFR $>10\%$ of baseline value within 3 days after administration of contrast media. However, sepsis was an independent risk factor. They concluded that in patients with renal impairment, administration of gadolinium based contrast media under sepsis milieu can induce acute kidney injury.

It is difficult to reach a firm conclusion regarding nephrotoxicity of gadolinium based contrast media. Ledneva et al,¹ in a review study, suggest that gadolinium chelates appear safe and non-nephrotoxic as intravenous contrast media for MRI or MRA in patients with normal renal function and in patients with preexisting renal insufficiency when used in doses similar to those recommended for MRI. However, deterioration in renal function may occur in the majority of cases after intraarterial administration of gadolinium based contrast media at doses higher than 0.2 mmol/kg for diagnostic or interventional angiographic procedures in patients with renal insufficiency (creatinine clearance <60 ml/min/1.73m²), which is frequently associated with DM and/or hypertension. Therefore, although high doses of gadolinium based contrast media (>0.2 -0.3 mmol/kg) are administered safely in patients with renal insufficiency, the clinical use of doses >0.2 mmol/kg should be avoided in these patients, especially when administered intraarterially.

NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Another complication after use of gadolinium contrast medium in patients with renal impairment, particularly in patients with GFR <30 ml/min/1.73m², is NSF. It is a fibroproliferative disease confined to patients with advanced chronic kidney disease and patients with acute renal injury and substantial renal insufficiency. The first case of this pathology was observed in

1997 and the disease was initially reported in 2000 in a case series of 14 patients undergoing hemodialysis.²⁸ Histologically, it is characterized by thickened collagen bundles, mucin deposition and the presence of CD34+/CD45RO+/type I procollagen+ and or CD68+/factor XIIIa+ cells in affected areas.²⁹

PATHOGENESIS

Transmetallation with dissociation of free gadolinium from its chelate has been suggested as a cause. Free gadolinium then binds with other anions such as phosphate, bicarbonate and deposits in tissues of patients with renal impairment. It then induces fibrosis through macrophage-induced phagocytosis and consequent release of cytokines and growth factors.³⁰ It has been suggested that spindle cells involved in NSF are circulating fibrocytes (CD 34/procollagen I positive cells) that are normally present in the blood and are involved in wound repair. These circulating fibrocytes would be aberrantly recruited to dermis in the absence of overt tissue injury.^{31,32} Other investigators observed the expression of transforming growth factor beta 1, which is a potent stimulus for the production of collagen I by some cell types and mediates interstitial fibrosis.³³

In an in vitro study,³⁰ whereby the effect of contrast agents on hyaluronan and collagen synthesis was observed, the following conclusions were reached. The linear gadolinium contrast agents (gadodiamide, gadoversetamide, gadopentetate dimeglumine and gadobenate dimeglumine) produce a maximum stimulation of fibroblast proliferation at a concentration of 0.1 mmol/L, with cell numbers increasing up to 2.3-fold after a 4-day exposure. The macrocyclic contrast agents (gadoteric acid and gadoteridol) produced a maximum stimulation of fibroblast proliferation at a concentration of 5 mmol/L and increase cell numbers up to 1.6-fold after 4 days of exposure. Finally, they suggested that not only free gadolinium but chelated gadolinium may also be bioactive in stimulating fibroblast proliferation meaning that all gadolinium-based contrast agents are associated with this risk when injected at high doses.³⁰

Among published cases of NSF, the interval between gadolinium administration and NSF onset has varied widely, from <10 days to 68 months; however, most patients developed NSF within 2 months after exposure.^{34,35} Several investigators have also suggested that a higher cumulative dose increases the likelihood of developing NSF.³⁴ Another study suggested that the volume and dose infused closely to the onset of symptoms correlated better with the incidence of NSF than cumulative volumes and doses over longer time intervals.²⁹ A number of other factors have been postulated to explain why some patients with severe chronic kidney disease who are exposed to gadolinium contrast media develop NSF and others do not. These include metabolic acidosis or medications that predispose patients to acidosis,^{36,37} increased iron, calcium and or phosphate levels,^{37,38} high dose erythropoietin therapy, immunosuppression,³⁹ vasculopathy,⁴⁰ an acute pro-inflammatory

event⁴¹ and infection.⁴² None of these potential risk factors have been demonstrated to be present in all affected patients. Therefore, none of these can be considered as a true co-factor with high degree of confidence.⁴³

Nephrogenic systemic fibrosis has also developed in patients with acute kidney disease,⁴⁴ even if renal function subsequently returned to normal following gadolinium based contrast media.⁴⁵ In one series, up to 20% of NSF cases were diagnosed in patients who had been in some degree of transient acute renal failure (often, but not always superimposed upon chronic renal disease) at the time of contrast media administration.⁴⁶

CLINICAL PRESENTATION

Nephrogenic systemic fibrosis typically manifests with extensive thickening and hardening of the skin with hyperpigmentation, plaques, papules and nodules and a peau d'orange appearance. It begins at distal extremities and may involve the trunk. The lesions are frequently erythematous, pruritic and /or painful. Restriction of joint movements results in progressive disability.²⁹ However, systemic involvement with fibrosis of other organs such as lung parenchyma, the pleura, pericardium, myocardium, diaphragm, kidneys, testes and striated muscle has been reported. Thus, this entity has been named "nephrogenic systemic fibrosis".⁴⁷ Other clinical findings are dyspnea, paresthesias and ocular manifestations, such as diplopia, uveitis and scleritis. The presence of cutaneous changes is associated with a 3-5-fold increased risk of dying.⁴⁸ Death is usually due to complications related to limited motility and respiratory failure.

GUIDELINES TO PREVENT NSF

According to a study⁴⁹ it is suggested that in order to minimize side effects of contrast media, the patients should be identified as high risk and noncontrast based imaging techniques should be used as long as they are suitable and safe. If the risk benefit ratio of the imaging information favors a contrast study, then use of contrast media of lowest complication risks should be used after obtaining informed consent, at a dose limited to 0.1 mmol/kg.⁵⁰

In a recent retrospective study in a large academic center, the incidence of NSF was determined after the adoption of administration guidelines for the use of restrictive gadolinium based contrast agent. These require (a) a recent serum creatinine level measurement in any patient who is aged 60 years or older and/or at risk for renal disease, (b) limiting the maximal weight-based dose administered to any patient with an estimated GFR (eGFR) <60 ml/min/m² to 20 ml, and (c) prohibiting the administration of gadolinium based contrast media in patients who have an eGFR <30 ml/min/m² and/or are undergoing chronic dialysis treatment (except in emergency situations). They concluded that after these restrictive guidelines were instituted, no new cases of NSF were identi-

fied.⁵¹ Similar results are reported in another study in which the authors observed a decrease of the incidence of NSF if gadolinium based contrast media were not administered to patients with creatinine clearance <30 ml/min/1.73m².⁵²

Specific recommendations for patients with end-stage renal disease on chronic dialysis have been proposed. In detail, if a contrast enhanced cross-sectional imaging study is required in an anuric patient with no residual renal function, it would be reasonable to consider administering iodinated contrast media and performing CT rather MRI. If a contrast-enhanced MRI must be performed, gadodiamide, gadopentetate dimeglumine and gadoversetamide should be avoided. Also, use of the lowest possible dose needed to obtain a diagnostic study is suggested and MRI examination should be performed as close to hemodialysis as possible. Many experts recommend that consideration should be given to the performance of several dialysis sessions following MRI examination, with use of prolonged dialysis times and increased flow rates and volumes. Peritoneal dialysis provides much less potential NSF risk reduction and should not be considered protective.⁴³

Additionally, for patients with chronic kidney disease (eGFR <30 ml/min/1.73m²) not on chronic dialysis or patients with eGFR of 30-44 ml/min/1.73m², it is recommended to avoid any contrast media either iodinated or gadolinium. If MRI contrast media administration is essential, use of lowest possible dose needed is recommended. Again, gadodiamide, gadopentetate dimeglumine and gadoversetamide should be avoided. It is suggested not to re-administer gadolinium based contrast media for several days to a week. For patients with eGFR of 45-59 ml/min/1.73m², risk of development of NSF is extremely small and it is recommended to use the lowest dose to obtain a diagnostic study. A decision to administer gadodiamide, gadopentetate dimeglumine or gadoversetamide should be made only following appropriate risk-benefit assessment. In patients with chronic kidney disease and eGFR of 60-110ml/min/1.73m², there is no evidence of increased risk of developing NSF. All gadolinium based contrast media can be administered safely in these situations.⁴³

Patients with acute renal failure are at risk of developing NSF. Gadolinium based contrast media should only be administered if it is absolutely necessary. If such an examination is required, then use of lowest possible dose needed is recommended and gadodiamide, gadopentetate dimeglumine or gadoversetamide should be avoided.⁴³

ALTERNATIVE TECHNIQUES

The concern about a possible link between gadolinium based contrast agents and NSF has stimulated further development of alternative techniques that do not require exogenous contrast media. Several such techniques have been developed.⁵³ An example of an alternative non contrast study to contrast induced MR angiography is reported in a recent study.⁵⁴ The use of rapid (quiescent-interval single shot) un-

enhanced MR angiography for the study of peripheral arterial disease in symptomatic diabetic population is suggested. Thus, according to the results of this study, quiescent-interval single-shot unenhanced MR angiography with a sensitivity of 92.1% and a specificity of 96.8% was an accurate non contrast alternative to contrast enhanced MR angiography for showing clinically significant arterial disease in patients with diabetes and symptomatic peripheral disease.

OTHER ACUTE ADVERSE REACTIONS OF GADOLINIUM BASED CONTRAST MEDIA

In addition to the side-effects already described, after administration of gadolinium based contrast media, other acute adverse reactions have also been observed. They are encountered with a lower frequency than that observed after administration of iodinated contrast media. The frequency of all acute adverse events after an injection of 0.1 or 0.2 mmol/kg of gadolinium chelate ranges from 0.07% to 2.4%. The vast majority of these reactions are mild, including coldness at the injection site, nausea with or without vomiting, headache, warmth or pain at the injection site, paresthesias, dizziness and itching. Reactions resembling an allergic response are very unusual and vary in frequency from 0.004% to 0.7%. A rash, hives or urticaria are the most frequent of these reactions and very rarely may bronchospasm occur. Severe life threatening anaphylactoid or non allergic anaphylactic reactions are extremely rare (0.001%-0.01%).⁴³ Fatal reactions may occur but are extremely rare. Overall, ionic linear gadolinium-based contrast agents have a significantly higher rate of immediate adverse events compared to nonionic linear gadolinium based contrast agents.⁵⁴

CONCLUSION

Use of gadolinium chelates in healthy individuals is safe and well tolerated by patients. Acute adverse reactions after administration of gadolinium based contrast media are rare. They are mild in severity. Death is extremely rare. However, contrast induced nephropathy is a complication after injection of gadolinium based contrast media in patients with renal insufficiency who also have other risk factors especially if a high dose is used. In patients with normal renal function these agents are safe and non nephrotoxic with a suggested dose of 0.1 mmol/kg. Another complication after the use of gadolinium contrast medium in patients with renal impairment, particularly in patients with GFR <30 ml/min/1.73m², is NSF, which is a fibroproliferative disease. Several guidelines have been developed in order to avoid contrast induced nephropathy and NSF and should be closely followed.

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