

# Complications from the use of intravenous gadolinium-based contrast agents for magnetic resonance imaging\*

*Complicações do uso intravenoso de agentes de contraste à base de gadolínio para ressonância magnética*

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**Abstract** Gadolinium-based contrast agents are much safer than the iodinated ones; however complications may occur and should be recognized for appropriate orientation and management. The total incidence of adverse reactions to contrast agents in magnetic resonance imaging ranges between 2% and 4%. Cases of severe acute reactions to gadolinium, such as laryngospasm and anaphylactic shock, are rare. Chronic complications secondary to the use of gadolinium also can occur and, recently an association between its use and a rare dermatologic disease occurring in patients with renal failure has been reported. Nephrogenic systemic fibrosis was the subject of an official health notification issued by the American Food and Drug Administration. This progressive disease is characterized by hardened skin with fibrotic nodules and plaques which may involve other parts of the body. Patients who have been affected by this disorder presented chronic renal failure, with metabolic acidosis and had been submitted to magnetic resonance angiography, probably involving exposure to large amounts of intravenous paramagnetic contrast. This review is aimed at presenting a succinct description of the gadolinium-based contrast agent types, possible secondary complications, their preventive measures and management.

*Keywords:* Magnetic resonance imaging; Gadolinium; Adverse reaction.

**Resumo** Os agentes de contraste à base de gadolínio são muito mais seguros que o contraste iodado, no entanto, existem complicações que devem ser reconhecidas, para orientação e tratamento adequados. A incidência total de reações adversas aos meios de contraste em ressonância magnética varia entre 2% e 4%. Casos de reações adversas agudas maiores ao gadolínio, como laringoespasm e choque anafilático, são raros. As complicações crônicas com o uso do gadolínio também existem e, recentemente, foi descrita associação entre seu uso e uma doença dermatológica rara que ocorre em pacientes com insuficiência renal. A fibrose nefrogênica sistêmica foi tema de anúncio público oficial pela agência americana de regulação de drogas, a Food and Drug Administration. Esta doença progressiva caracteriza-se pelo espessamento e endurecimento da pele e fibrose, que podem acometer outras partes do corpo. Os pacientes que desenvolveram esta complicação apresentavam insuficiência renal crônica, estavam em acidose metabólica e foram submetidos a angiografia por ressonância magnética, provavelmente com injeção de grande volume de contraste paramagnético. Esta revisão tem o objetivo de apresentar uma descrição sucinta dos tipos de meios de contraste à base de gadolínio, possíveis complicações e medidas para prevenção e tratamento destas.

*Unitermos:* Imagem por ressonância magnética; Gadolínio; Reação adversa.

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## INTRODUCTION

Most of contrast agents utilized in magnetic resonance imaging (MRI) are based on paramagnetic gadolinium (Gd) chelates which have been utilized since the late eighties<sup>(1)</sup>. Some unofficial estimates account for approximately 90 million doses already delivered worldwide.

The types of Gd-based contrast agents currently in the market may be divided into two categories: non-specific extracellular, and specific intracellular contrast agents,

whose main difference is represented by the chelating molecule carrying the gadolinium. Generally, it is considered that gadolinium-based contrast agents are much safer than iodinated contrast agents utilized in conventional radiology and computed tomography (CT); however, there are complications that should be recognized for an appropriate management and pre- and postprocedural guidance.

The present review is aimed at presenting a succinct description of Gd-based contrast agent types, possible complications,

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their preventive measures and management.

### GENERAL CONSIDERATIONS ABOUT USE OF INTRAVENOUS CONTRAST AGENTS FOR MRI, AND Gd-BASED CONTRAST AGENTS TYPES

In the Nature, gadolinium is found as a rare mineral, a chemical element difficult to extract, and presents like a silvery white crystal. At room temperature, it is one of few metals with ferromagnetic properties. Gadolinium applications include microwave ovens, TV sets and other electronic components. In medicine, Gd is utilized solely in the form of solution compounds for radiological images enhancement.

The expected and, consequently, most significant effect from Gd as a contrast agent for MRI is the reduction in the T1 relaxation time in tissues where the compound is found. It is interesting to observe that MRI images do not demonstrate the Gd itself, but its paramagnetic effect on the surrounding tissues. Generally, most of Gd-based contrast agents present a distribution in the body similar to the one presented by iodinated contrast agents. However, it has been already evidenced that MRI sensitivity to gadolinium is higher than the CT sensitivity to iodinated contrast agents. Usually, the mean dose of intravenous contrast delivered during MRI examinations ranges between 10 ml and 20 ml. This dose is 5-15-fold lower than the one utilized at iodinated contrast-enhanced CT, and certainly this is one of the reasons for which the use of Gd is safer.

Additionally to the factor related to the injection dose, other factors are extremely significant in the evaluation of a contrast agent safety, and are associated with the inherent compound toxicity, circulation stability, and degree of clearance in the human body. The Gd ion, while free in the blood circulation, is quite toxic, with biological half-life of some weeks, i.e., much longer than the one presented by Gd chelate compounds, which corresponds to approximately 1.5 hour<sup>(2,3)</sup>. The Gd ion, when chelated with a molecule, presents an altered pharmacokinetics, accelerating its clearance and, therefore, remarkably reduc-

ing its relative toxicity<sup>(3)</sup>. The chelation of gadolinium allows an increase of up to 500 times in the rate of renal excretion. It is the chelating agent that differentiates the several Gd-based contrast agents found in the market.

Some other characteristics directly affecting the safety of these agents are: ionic *versus* non-ionic molecular structure (the non-ionic one is preferable); osmolality (the lower the osmolality, the higher the safety) and viscosity (a low viscosity is preferable, influencing the contrast injection rate). Chart 1 shows a summary of these characteristics for some of the currently utilized gadolinium-based contrast agents. One can say that molecular structure and osmolality are less significant as far as safety is concerned in the comparison between gadolinium-based and iodinated contrast agents, considering the lower injection dose utilized at MRI.

Additionally, regarding paramagnetic contrast agents safety, the most relevant factor is stability, i.e., the resistance to the contrast agent breakdown into its components, releasing Gd ions into the blood circulation. Currently, the most stable Gd chelating agents are Magnevist and MultiHance. Magnevist is the most extensively utilized and therefore the most clinically tested contrast agent. Former reports describe the safety of Magnevist in different populations, including patients with chronic renal failure<sup>(4,5)</sup> and pediatric patients<sup>(6)</sup>. MultiHance presents two times the T1-relaxation time of other chelating agents, meaning that half a dose of MultiHance presents the same effect of other contrast agents, and that this may represent an alternative approach for reducing the amount of contrast agent delivered, as necessary. On the other hand, Primovist<sup>®</sup> causes a reduction in the relaxation time in a much higher degree than MultiHance does. However, Primovist is relatively new in the European market and is still to be approved for use in the United States. Both MultiHance and Primovist present mixed clearance (renal/hepatic), the excretion via hepatocytes affecting significantly the characterization of hepatic lesions, although its utilization is not excluded for dynamic studies of other organs after rapid injection.

### Gd-BASED CONTRAST AGENTS COMPLICATIONS

#### Acute adverse reactions

Adverse, acute reactions to gadolinium may be classified into major or severe and minor, and subdivided into local and general. The total incidence of adverse reactions to MRI contrast agents ranges approximately between 2% and 4%.

Most frequently, minor, general reactions are nausea, emesis, hives, headache, while local reactions are: skin irritation, itching and coolness.

A transitory increase may occur in the bilirubin (Magnevist, 3% to 4% of patients) and iron serum levels (with Magnevist and Omniscan<sup>™</sup>, completely recede within 24-48 hours). The passage of Gd-based contrast agents through the placenta and into the milk during lactation has been already demonstrated, so it is recommended that these contrast agents are not utilized in pregnant women.

Cases of major acute adverse reactions to Gd, such as laryngospasm and anaphylaxis rarely occur<sup>(7)</sup>. A 0.01% incidence of anaphylactoid reactions to Gd-based contrast agents is reported, while for ionic iodinated contrast agents the incidence achieves 0.17%. Adverse reactions following intravenous Gd-based contrast agent injection are more frequent in patients with previous history of reaction to either Gd-based or iodinated contrast agents<sup>(8)</sup>. Sixteen of 75 (21%) patients who presented allergic reaction to Gd presented a new reaction following subsequent injections<sup>(9)</sup>. Patients with previous reaction to iodinated contrast agents have more than twice the chance of presenting allergic reaction to Gd, with 6.3% incidence in a study with 857 patients<sup>(10)</sup>. Patients with asthma also present a higher probability of developing adverse reaction to Gd. Generally, patients with previous history of allergies, present an increased risk for adverse reactions, approximately 2-3.7 times higher than those without a history of allergy.

Patients with a previous history of allergy to any type of intravenous contrast or with history of other allergies may benefit from the adoption of a premedication scheme with corticosteroids and anti-histamines, and should be more closely fol-

## Complications from the use of intravenous gadolinium-based contrast agents

**Chart 1** Physical-chemical features of commercially available MRI contrast agents.

Contrast agents	Generic names	Gd-DTPA – gadopentetate dimeglumine (0.5 mol/l)	Gd-DOTA – gadoterate meglumine (0.5 mol/l)	Gd-HP-DO3A – gadoteridol (0.5 mol/l)	Gd-DTPA-BMA – gadodiamide (0.5 mol/l)	Gd-BOPTA <sup>†</sup> – gadobenate dimeglumine (0.5 mol/l)	Gd-DO3A-butrol – gadobutrol (1.0 mol/l)	Gd-DTPA-BMEA – gadoversetamide (0.5 mol/l)
	Trademarks*	Magnevist Magnograf <sup>®</sup> Viewgam <sup>®</sup>	Dotarem <sup>®</sup> Artirem <sup>®</sup>	ProHance	Omniscan	MultiHance	Gadovist <sup>®</sup>	OptiMARK <sup>®</sup>
Features	Molecular structure	Linear, ionic	Cyclic, ionic	Cyclic, non-ionic	Linear, non-ionic	Linear, iônica	Cyclic, non-ionic	Linear, non-ionic
	Thermodynamic stability constant (log <i>K</i> <sub>eq</sub> )	22.1	25.8	23.8	16.9	22.6	21.8	16.6
	Conditional stability constant pH 7.4	18.1	18.8	17.1	14.9	18.4	–	15.0
	Osmolality (osm/kg)	1.96	1.35	0.63	0.65	1.97	1.6	1.11
	Viscosity (mPa·s at 37 °C)	2.9	2.0	1.3	1.4	5.3	4.96	2.0
	Relaxation T1 (l/mmol/s) 0.47 T, plasma	4.9	4.3	4.6	4.8	9.7	5.6	Not available
	Metal chelate (mg/ml)	469	278.3	279.3	287	334	604.7	330.9
	Chelating excess (mg/ml)	0.4	–	0.23	12	–	–	28.4

\* Trademarks mentioned herein are for identification purposes only, not reflecting any preference or presentation of a definite list of the whole range of products currently in the market. Also for this reason, the names of companies involved in their production and commercialization are not included herein. <sup>†</sup> It is considered as an organ-specific agent (but non-exclusive) because of the mixed renal/biliary clearance, with utilization especially during hepatic MRI studies.

lowed-up during the Gd injection, as well as remaining in observation for a longer period following the paramagnetic contrast injection<sup>(8)</sup>. However, it is important to note that the premedication validity is still controversial, even in cases of iodinated contrast agents<sup>(11)</sup>.

As regards the incidence of minor complications, also there is a relatively great difference, quantitative and qualitatively greater with iodinated contrast agents for CT. However, complications from the use of Gd can occur and, most recently, a possible association between its use and a rare dermatological disease has been described in patients with renal failure<sup>(12,13)</sup>. This association has been the subject of an official Health Notification issued by the American Food and Drug Administration (FDA), recommending to the companies involved in the production of Gd-based contrast agents the addition of a warning on nephrogenic

systemic fibrosis on the packages of these products<sup>(14)</sup>. A problem that previously seemed to be minor and restricted, increasingly seems to represent a real complication that must change the conduct in the use of these agents. This subject is furtherly discussed below.

### **Nephrogenic fibrosing dermatopathy (NFD)/nephrogenic systemic fibrosis (NSF) and Gd-based contrast agents in patients with severe renal disease**

A recent study has reported that, in a four-year period, 20 patients in Denmark and five in Austria developed a rare disease found exclusively in patients with a severely decreased renal function. All of these patients had received Omniscan for MRI-angiography few weeks or months before the disease onset. About 17500 patients undergo examination with Omniscan per year in Denmark. Since January 2002,

approximately 400 patients with renal failure have been examined, and 20 (5%) of them have developed NFD.

NFD, mostly known as NSF, was first diagnosed in 1997, and formally described in 2000<sup>(15)</sup>. This disease is associated with increased collagen deposition, causing thickening and hardening of the skin (predominantly involving distal extremities, although the trunk may be involved) and fibrosis affecting other regions of the body, including diaphragm, heart, pulmonary vasculature and thigh muscles. There is no definite cure, despite scarce studies reporting a partial response to several therapies such as plasmapheresis, extracorporeal and thalidomine. Data in the literature suggest delay, or even reversion of symptoms with improvement in the renal function. The disease is progressive, and may be fulminant in about 5% of cases, sometimes leading the patient to death.

A recent article published in the journal *Nephrology Dialysis Transplantation* describes the development of NSF associated with the use of Omniscan in five patients with renal failure<sup>(13)</sup>. Patients with this progressive and, as far as it is concerned, irreversible disease, develop fibrosis in several organs likely resulting in severe joint contractures secondary to skin fibrosis. The patients described in this article presented chronic renal failure, undergoing metabolic acidosis, and had been submitted to MRI-angiography, probably with injection of a high dose of paramagnetic contrast agent. Later, another article was published in Europe, reporting the occurrence of da NSF in a similar group with 13 patients, also following the administration of Omniscan<sup>(12)</sup>. Clinical aspects highlighted in the Health Notification issued by the FDA are the presence of chronic renal failure and the utilization of high doses of Gd. The FDA informs that is currently evaluating the whole spectrum of Gd-based contrast agents and not only Omniscan<sup>(14)</sup>, although all reports are specifically regarding this contrast agent. Up to this moment, possible interactions between other prescribed drugs and Omniscan still remain unknown. Still unpublished studies developed in several American institutions suggest that the development of NSF secondary to Gd-chelating agents is not rare and, as far it is concerned, is related exclusively to Omniscan injection. The onset of this condition typically occurs 16 days after the contrast agent injection, and this prolonged period can explain why this correlation has not been previously described. Although these patients have been probably submitted to MRI-angiography with high gadolinium doses (a method lacking FDA approval), the use of Omniscan should be prudently avoided in patients with chronic renal failure until new data recommend otherwise.

#### **MRI contrast agents use in patients with renal failure**

After intravenous Gd-based contrast agent injection, intravascular copper and zinc (typically found in minor amounts in the blood), which present a chelate affinity competitively displace part of Gd from the chelating molecule as the diethyltri-amine penta-acetic acid (DTPA), releasing

the free Gd ion ( $Gd^{+3}$ ). Despite the high Gd toxicity, the total free Gd concentration is very low and is very rapidly eliminated, allowing the maintenance of the free ion concentration. As a matter of fact, in patients with a normal renal function, the dissociation rate is lower than the clearance rate, preventing the occurrence of any accumulation phenomenon. Also, it is believed that macrocyclic Gd-chelates tend to be more stable than the linear ones.

As new physiological sources of copper and zinc ions migrate into the intravascular space in an attempt to recover their concentration balance, they also displace more Gd than chelate. This cycle proceeds until all the Gd chelate is eliminated from the body by the kidneys through glomerular filtration. For this reason, there is a potential concern regarding the level of free Gd ion in cases of renal failure, as well as in patients with a lower clearance rate. The safety of Gd-based contrast agents for patients with renal function disorders or severe renal failure is still to be established. Some studies in the literature suggest a reasonable tolerability to this type of contrast agents by these patients.

Magnevist is dialyzable, with more than 95% of the delivered dose being removed at the third dialysis session.

#### **Other relevant adverse collateral effects**

Pseudo-hypocalcemia has been reported with the use of less stable contrast agents like Omniscan and OptiMARK<sup>®</sup>, but not with Magnevist and MultiHance, although additional researches are currently in development about this subject<sup>(16)</sup>. It is important to understand the so called "pseudo-hypocalcemia is observed exclusively at laboratory (calorimetric) studies, occurring only within 24 hours following the contrast agent injection. The relevance of understanding this problem resides in the necessity of differentiation between pseudo- and real hypocalcemia, avoiding the inappropriate management with calcium replacement, a therapy that has already been reported as causative factor for death in at least one case<sup>(16)</sup>.

Differently from iron, or even manganese - another element also utilized as paramagnetic contrast agent -, free gadolinium is not typically present in the human body,

and is extremely toxic. Free Gd is analogous to calcium and can be deposited on developing bones — in this case, the greatest deal of concern is raised regarding developing fetuses and children. Although long term outcomes from calcium deposition during gestation still remain unknown, this is something that should raise concern. Omniscan instructions include the description of skeletal malformations in rat fetuses at the second gestational trimester, most probably because of maternal toxicity<sup>(17)</sup>. Another question is what occurs with free chelating. The free chelating can "chelate" other cations besides calcium in a process described as transmetallation<sup>(18)</sup>. Transmetallation may lead to the development of severe diseases in animal models, but the effects on humans from relatively low doses generally utilized are still to be clearly defined<sup>(19)</sup>.

#### **PRESENT PRECAUTIONARY MEASURES IN THE PRESCRIPTION Gd-BASED CONTRAST AGENTS FOR INTERNAL USE**

1 – Use in patients with renal failure should be avoided, at least until the actual role of these agents in the development of NSF is established. For this purpose, it is necessary to identify the patients under the risk for NSF, according to FDA recommendations: a) severe acute or chronic renal failure (glomerular filtration rate < 30 ml/min/1.73 m<sup>2</sup>); b) acute renal dysfunction associated with hepato-renal syndrome or during perioperative period of liver transplantation. Contrast agents to be avoided are: Omniscan, Magnevist and OptiMARK. However, it would be prudent to consider any Gd-based contrast agents until new evidences are found. In case of necessity of contrast-enhanced MRI in these patients, the lowest dose possible should be considered, besides hemodialysis immediately after the procedure (the ideal approach would be three hemodialysis sessions in consecutive days).

2 – Gadolinium should not be utilized in replacement of iodinated contrast agents, except if absolutely necessary and after monitoring of creatinine, with scheduling of repeated hemodialysis sessions, as necessary.

3 – Avoid the use in pregnant women and children.

4 – Consider the possibility of premedication with corticoid and anti-histamine in patients with previous history of allergic reaction to contrast agents of any type or history of severe allergy.

Finally, it is important to differentiate gadolinium-based from iron-based and manganese-based contrast agents which present more restricted indications, with other types of complications, and which are much less utilized in the daily routine of MRI centers worldwide. In Brazil inclusive, such contrast agents either have not been introduced yet, or have a quite restricted use because of their high cost.

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