Curr Treat Options Allergy (2020) 7:32–42
DOI 10.1007/s40521-020-00239-x

Anaphylaxis (M Sanchez-Borges, Section Editor)

Anaphylaxis Induced by Magnetic Resonance Imaging (MRI) Contrast Media

Ana Rosado, MD
Ana Gonzalez-Moreno, MD
Martina Privitera-Torres, MD
Miguel A Tejedor-Alonso, MD, PhD[*]

Address
[*]Unidad de Alergia. Hospital Universitario Fundación Alcorcón, C/Budapest 1, 28922, Alcorcón, Madrid, Spain
Email: MATejedor@fhalcorcon.es

Published online: 30 January 2020

This article is part of the Topical Collections on *Anaphylaxis*

Keywords Anaphylaxis · Gadolinium-based contrast agents · Paramagnetic contrast · MRI contrast media · Allergic reaction

Opinion statement

Purpose of review The aim of this document is to review the epidemiology, diagnosis, and treatment of immediate and anaphylactic reactions to gadolinium-based contrast agents (GBCA) most commonly used in magnetic resonance imaging (MRI).
Recent findings The frequency of adverse reactions to GBCA ranges from 0.04 to 2.2%. Most reactions are mild (47%–95%) and the frequency of anaphylactic shock is 0.004%–0.01%. Mortality due to anaphylaxis induced by GBCAs has been 0.0019%.
Allergic reactions are more frequent in patients with a previous reaction, in females, using macrocycle estructure GBCA and with hepatic, abdominal, and thoracic examinations. Determination of tryptase in the acute phase, and allergy study could confirm the culprit drug and assess the use of an alternative GBCA.
Allergic reactions, including anaphylaxis, can be resolved with appropriate training, early identification, and suitable equipment, especially in radiology departments.
Summary Anaphylaxis to GBCA is extremely rare. A history of previous reactions to GBCA is the main risk factor for a new reaction. In patients who have previously experienced a reaction, it is recommended to perform an allergological study to establish or rule out allergy to GBCAs and to assess the use of an alternative GBCA if necessary.

Introduction

Use of gadolinium-based contrast agents in clinical practice

Gadolinium-based contrast agents (GBCAs) are widely used in clinical practice. Some authors estimate that they have been administered to more than 100 million patients throughout the world [1, 2•]. The safety of these agents has been thoroughly assessed during the last 10–20 years in powerful, mainly retrospective, observational studies covering thousands of administrations of GBCA.

Incidence of immediate reactions to GBCA

The frequency of adverse reactions to GBCA ranges from 0.04% to as much as 2.2% [1, 3, 4, 5••]. The true prevalence is probably close to 0.1% [2•]. In other words, the incidence of adverse reactions to GBCAs is low (1 per 10,000–40,000 injections) [1]. Other authors report the prevalence to be 1 per 1000 injections [2•, 3]. Therefore, the prevalence of adverse reactions to GBCAs is 10 times lower than that of adverse reactions to iodinated contrast agents [6].

The prevalence of adverse reactions in children is lower than in the general population [7••, 8, 9•]. Dillman et al. [10] reported an incidence of 1. Eight reactions per 1000 injections in a large pediatric cohort. Davenport et al. [11] reported 0.5 reactions per 1000 injections, and Forbes-Amrhein et al. [9•] found a frequency of 0.06%.

These differences between studies have several explanations. First, more large-scale studies have been performed with older products than with younger products, for which samples are small. Second, differences in the methodology used to collect data, even for the same agent, could result in contradictory results. Third, some studies include data on very few products. Finally, some studies report the overall number of adverse reactions, including physiological and allergic reactions, whereas others report only allergic reactions [5••].

Several studies report differences in the frequency of reactions to GBCAs, although these differences are not statistically significant [3]. Nevertheless, based on data from 105 magnetic resonance imaging (MRI) facilities and 800,000 administrations of GBCA, Murphy et al. [12] reported gadodiamide (a nonionic linear agent) to be substantially safer than gadopentetate dimeglumine (ionic linear GBCA) and gadoteridol (macrocyclic GBCA). This observation is consistent with the fact that nonionic iodinated contrast agents are associated with lower adverse events and mortality rates than ionic agents [8, 13]. Three additional studies report higher frequencies of immediate hypersensitivity reactions for gadobenate dimeglumine than for gadopentetate dimeglumine [5, 14, 15].

Severe reactions are rare (1%–10%), although in most cases the prevalence is higher than 5% [2•, 5, 6, 7••, 9•, 10, 13, 14, 16•, 17•, 18, 19]. Most reactions are mild (47%–95%), and in almost all studies mild reactions accounted for 75% of all reactions [2•, 5••, 6, 7••, 8, 9•, 10, 13, 14, 16•, 17•, 18–20].

The reported frequency of anaphylactic shock is 0.004%–0.01% [5••, 7••]. Mortality due to anaphylaxis induced by GBCAs has been reported to

be 0.0019%, and the death rate reported to the U.S. Food and Drug Administration is 0.00008% (40 deaths in 51 million injections of MRI contrast media from 2004 to 2009) [5••, 8].

Classification of contrast media used in MRI

The different types of contrast agents used in MRI can be classified according to the following [21]:

1. Molecule morphology
   - Linear
   - Cyclic
2. Magnetic susceptibility
   - Paramagnetic
   - Ferromagnetic
   - Superparamagnetic
3. Target tissue
   - Extracellular nonspecific
   - Specific tissue
4. Physicochemical characteristics
   - Ionic vs nonionic
   - Iso-osmolar

The contrast media most commonly used in MRI are based on gadolinium (GBCA), which is a paramagnetic substance [22]. All contrast media whose base is gadolinium contain a chelating agent with linear or cyclic morphology that limits toxicity in the body [18, 23].

The most frequently used contrast agents are summarized in Fig. 1.

Ionic complexes with a cyclic structure have proven to be the most stable and, therefore, the least likely to release ionic gadolinium into the body, while the least stable are nonionic linear agents [22].

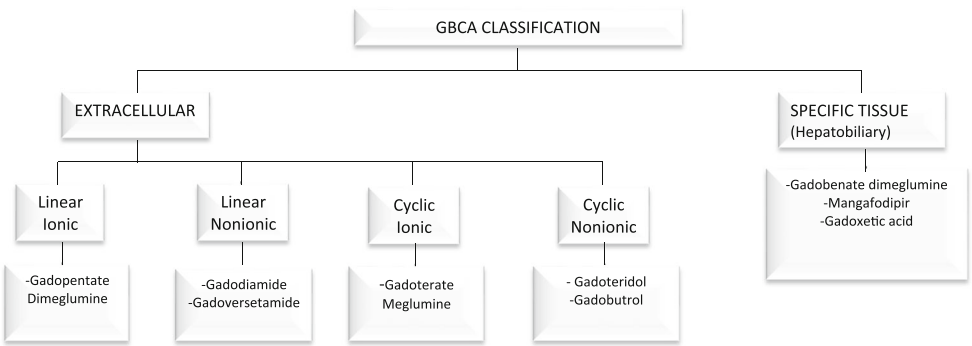

Fig. 1. GBCA Classification in MRI.

Manganese chelates are used specifically as hepatobiliary contrast media, and iron contrasts are used when it is necessary to shorten the T2 signal. Oral contrasts are rarely used due to their high cost [24•].

Pathophysiology

In some studies, a positive prick test result suggests an IgE-mediated mechanism as the cause of immediate reactions to GBCAs [25•]. However, in other cases, the high osmolality of the chemical structure of GBCAs, direct complement activation, and bradykinin formation can result in mast cell and basophil degranulation, with release of histamine and other mediators. All of these mechanisms may cause adverse reactions [8, 13].

Risk factors associated with immediate reactions to GBCA

Up to 50% of patients who receive GBCAs have risk factors, that is, conditions that increase the frequency of immediate adverse reactions [10, 14, 17•]. These risk factors are very similar to those associated with iodinated contrast agents [14].

The main risk factor is a previous reaction to a GBCA. Up to 30% of patients who experience an adverse reaction have previously experienced a reaction [14].

Repeated exposure to GBCAs [26, 27] and a history of severe previous reaction (up to 20% of patients) [5••] are significant risk factors (up to eightfold greater) for a severe adverse reaction [7••, 19, 27]. However, cases of anaphylaxis without previous exposure have been reported [2•].

GBCAs with a macrocyclic structure carry a higher risk of adverse reactions (16 per 10,000 doses) than those with a linear ionic estructure (8.5 per 10,000 doses) or a linear nonionic structure (1.5 per 10,000 doses) [28••]. These differences may imply increased binding capacity to certain proteins.

A study of 194,400 injections revealed significant differences between GBCAs. The drugs that most frequently induced adverse reactions were gadofosveset, gadoxetate, gadobenate, and gadopentetate [5••], although only patients who had received gadobenate dimeglumine experienced anaphylactic shock. In a recent meta-analysis, the order from greater to lesser frequency of allergic reactions was similar, with the greatest frequency recorded for gadofosveset, followed by gadoxetate, gadobenate, gadoteridol, gadobutrol, gadopentetate, and gadodiamine. The rate of severe reactions was greater with gadoxetate, gadofosfoveset, and gadobenate than with gadopentate [28••]. In another study [29], gadobenate was associated with infrequent but more severe reactions that were not prevented with premedication.

Studies based on a large number of injections (> 20,000) revealed that no patients died [3, 29].

No significant relationships were found between age and frequency or severity of the reactions.

Adverse reactions have been shown to be more frequent in females than in males (71.6% vs 28.4%) (risk ratio 1.7) [2•, 5••, 8, 14, 17•, 18], and severe adverse reactions are also more frequent in females (3/5) and in

outpatients. However, sex did not affect the level of severity of the reactions in some studies [5••], although data reported by Jung et al. [26] suggested that severe adverse events are more likely to be fatal in male patients.

Adverse reactions are more frequently associated with hepatic, abdominal, and thoracic examinations (0.17%, 0.16%, and 0.15%, respectively) than with cerebral and spinal procedures. The lowest rate of adverse reactions (0.14%) was recorded in examinations of the limbs [5••].

A history of asthma, rhinitis, and food or drug allergy is a more controversial risk factor, owing to the inclusion in a broad group of illnesses with varying pathogenesis, epidemiology, and natural history [14]. In patients with a history of asthma and drug allergies, the risk of an adverse event increases 1.5 to 1.9 times [8]. Allergic disease or atopy is found in 40% of patients with severe reactions [5••], although in well-controlled asthmatic patients, the risk is not increased [1]. Severe dermatitis, urticaria, and anaphlylactic reactions to drugs and foods increase the risk of severe adverse reactions [13].

The severity of the reaction can be affected by preexisting conditions such as multiple myeloma (due to the interaction between light chains and GBCAs), mastocytosis, autoimmune disease, viral infections, treatment with IL-2, and serum creatinine > 2 mg/mL [8].

Power injection has been considered a potential risk factor [13], and manual injection requires a member of hospital staff to be near the patient in order to identify and treat reactions early. Aran et al. [5••] found that a power injection was administered in 50% of patients who experienced adverse reactions and in 80% of those who experienced a severe adverse reaction.

Adverse reactions can occur despite premedication with corticosteroids and antihistamines. Premedication is only recommended for patients with a previous history of moderate or severe adverse reactions [13, 15].

Clinical manifestations

The clinical manifestations of an allergic-like reaction to a GBCA are similar to those of a reaction to iodinated contrast media. However, clinical manifestations are uncommon and less severe and vary in frequency from 0.004 to 0.7% [14, 30].

Allergic-like reactions are classified as mild, moderate, and severe. Mild allergic reactions such as urticaria/pruritus, limited cutaneous edema, limited itchy throat, nasal congestion, sneezing, conjunctivitis, and rhinorrhea are self-limiting. Moderate reactions require medical management. These include urticaria/pruritus, erythema with stable vital signs, facial edema without dyspnea, throat tightness or hoarseness without dyspnea, wheezing/bronchospasm, and mild or no hypoxia. Severe reactions are considered life-threatening and require immediate medical attention. These include diffuse edema, facial edema with dyspnea, diffuse erythema with hypotension, laryngeal edema with stridor and/or hypoxia, wheezing/bronchospasm, significant hypoxia, and anaphylactic shock (hypotension with tachycardia) [6, 31]. Urticaria is the most common clinical manifestation of allergic reactions to GBCAs (50%–90%).

Severe life-threatening anaphylactic reactions are extremely rare (0.001% to 0.01%) [17•, 32]. Most anaphylactic reactions to contrast media occur immediately after the injection (30 min–1 h) [17•].

Anaphylactic reactions to GBCAs

The cases of severe anaphylaxis induced by GBCAs presented below highlight the severity of some reactions:

One severe reaction was documented in a 50-year-old woman who had previously received GBCAs without reactions [14]. The patient experienced an allergic-like reaction in which iodinated agents and other drugs were identified as potential risk factors. The reaction manifested as dyspnea and swelling 8 min after injection, and the patient remained in the intensive care unit until she was discharged, without sequelae.

A 64-year-old woman with previous cardiovascular disease but no history of atopy, asthma, or drug allergy experienced fatal anaphylaxis 2 min after her first exposure to gadobenate [18]. The reaction manifested as hypotension, loss of consciousness, bradycardia, and oxygen desaturation. Despite therapy with epinephrine, hydrocortisone, dexchlorpheniramine, and resuscitation, the patient developed a bleeding diathesis and eventually died. Serum tryptase was elevated (63 ng/mL), thus confirming the diagnosis.

Kounis syndrome induced by GBCAs [33] has been reported in a 78-year-old patient with hypertension and no previous history of heart disease or allergy. Immediately after injection of gadopentetate dimeglumine, the patient began to experience chest pain with ST elevation, dyspnea, decreased level of consciousness, and bradycardia. Examination of the coronary arteries confirmed no critical stenosis. In another case of Kounis syndrome attributed to GBCAs, the patient had previous drug allergies [34].

Cardiac arrest has been reported after gadobenate dimeglumine injection [35]. The patient was a 76-year-old woman with no previous history of allergy who had tolerated GBCAs on other occasions. She had a history of hypertension, cardiovascular disease, and hypothyroidism. Immediately after injection of contrast agent, she experienced respiratory distress and two episodes of cardiac arrest that resolved after resuscitation. The main complications after the episode were anuria, polyneuropathy, and ischemic colitis. The highest tryptase level after the reaction was 73 μg/L, thus confirming the diagnosis of anaphylactic reaction.

Acute abdominal pain is an unusual presentation of an anaphylactic reaction [23]. A 48-year-old woman presented with sudden and intense abdominal pain followed by hypotension immediately after injection of a GBCA. The reaction took the form of pruritus and generalized maculopapular rash and resolved with epinephrine, methylprednisolone, diphenhydramine, and famotidine. The patient reported an imprecise allergic reaction to iodinated contrast medium 15 years before.

Prince et al. [36] reported the case of another fatal reaction caused by power injection of a GBCA, in which the cause was the absence of early recognition and treatment (medical staff were not present in the room).

In a recent case, a 42-year-old woman experienced cardiac arrest after receiving gadobutrol. Resuscitation was performed for 1 h, and the patient was

transferred to another hospital, where she experienced fatal neurological damage. Her tryptase level was 200 μg/L [37].

Diagnosis

During an acute systemic reaction, it is always useful to measure serum tryptase in order to confirm anaphylaxis and make a comparison with a previous basal measure or a level taken at least more than 25 h after the reaction [18, 35, 37].

Once the reaction has resolved, the patient will have to undergo further diagnostic tests to confirm the allergy. Alternative agents can then be considered.

Clinical history

Data on the reaction are very important. It is essential to record the GBCA administered, the interval between administration of the GBCA and the onset of symptoms, clinical features, and the treatment required to control the reaction.

Skin tests

For immediate reactions, skin tests should be performed within 2–6 months after the reaction; the number of positive skin test results after this period will be lower. Prick and intradermal tests should be performed in immediate reactions [17•]. Clinical guidelines on skin testing with iodinated contrast media are clearer than those on GBCAs. Nevertheless, current recommendations are in favor of undiluted GBCAs for skin prick tests and dilutions of 1:1000–1:10 for intradermal tests. Undiluted GBCAs may prove irritant in intradermal testing and yield false-positive results [2•].

In vitro methods

The basophil activation test and leukocyte histamine release test are used in acute hypersensitivity reactions [38–40].

There is in vitro evidence that some preparations of MRI contrast media are able to induce mast cell degranulation in vitro, although there is no information on the underlying differences in the mechanisms of susceptibility to a putative direct mast cell effect [41].

Drug provocation tests

The drug provocation test (DPT) is considered the gold standard for the diagnosis of drug hypersensitivity reactions.

In the case of severe reactions, an alternative GBCA can be tried to verify tolerance. If the test result is positive with the culprit agent, an alternative GBCA should be sought [35–42].

The DPT is performed by administering increasing doses of the GBCA at 45–60-min intervals.

Alternatives/cross-reactivity

Cross-reactivity between gadolinium chelates remains unclear [38, 43, 44]; however, there does not seem to be cross-reactivity between macrocyclic and

linear substances. One case report suggested cross-reactivity between macrocyclic compounds [45]. Therefore, in the case of an immediate reaction confirmed by a positive skin test result with the culprit GBCA, a DPT should be performed using a GBCA that gave a negative skin test result.

Treatment

Acute hypersensitivity reactions, including anaphylaxis, should be treated as soon as possible. Radiology departments should have appropriate medications and equipment, as well as staff trained in the management of anaphylaxis.

If symptoms appear, the GBCA infusion should be interrupted. Mild reactions (limited cutaneous urticaria/erythema, itchy throat, and sneezing) may be self-limiting and require no treatment, although patients should be monitored for up to 1 hour after administration [46]. Some authors propose that mild reactions should be treated with anti-H_1 blockers.

Moderate reactions (diffuse cutaneous urticaria/erythema, facial edema or throat tightness without dyspnea, or bronchospasm/wheezing without hypoxia) and severe reactions (with signs of cardiovascular compromise, such as hypoxia, hypotension, and tachycardia) must be treated immediately, according to international guidelines [47]. Bronchospasm should be treated with oxygen and an inhaled β_2-agonist. Anaphylactic reactions require treatment with epinephrine.

The most common premedication protocol used is 50 mg of prednisone administered orally 13, 7, and 1 h before the examination and 5 mg of intravenous diphenhydramine 1 h before the examination.

Power et al. [14] reported the frequency of allergic-like reaction to be 36.4% despite premedication on a per-patient basis; Jung et al. [26] reported that 36% of premedicated patients experienced an allergic reaction and that 25% of patients without premedication experienced a reaction with a subsequent administration of a GBCA. Some studies show that premedication can reduce the frequency of mild reactions but not moderate or severe reactions.

If the reaction is mild or moderate, it may be reasonable to carry out subsequent procedures with a different GBCA. The decision to administer an alternative agent is facilitated by skin testing and DPT.

Conclusions

The incidence of adverse reactions to GBCAs, especially allergic reactions, is very low. Nevertheless, severe adverse reactions such as anaphylaxis do occur and may be fatal.

A history of previous reactions to GBCA or to iodinated contrast agents is the main risk factor for a new reaction to a GBCA, although in 30% of patients, the reaction can appear at the first exposure to the GBCA.

Identification of potential risk factors and previous health problems and recognition of the initial symptoms of a reaction can minimize harm for the patient. Allergic reactions can be resolved with appropriate training, early identification, and suitable equipment.

Determination of tryptase is recommended to confirm an allergic reaction.

Nonionic GBCAs may reduce the frequency of allergic reactions and should, therefore, be recommended in patients at risk.

In patients who have previously experienced a reaction, it is recommended to perform an allergological study to establish or rule out allergy to GBCAs and to assess the use of an alternative GBCA if necessary.

Compliance with ethical standards

Conflict of interest

Ana Rosado, Ana Gonzalez-Moreno, Martina Privitera-Torres, and Miguel Tejedor-Alonso declare no conflicts of interest relevant to this manuscript.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Beckett KR, Moriarity AK, Langer JM. Safe use of contrast media: what the radiologist needs to know. Radiographics. 2015;35(6):1738–50. https://doi.org/10.1148/rg.2015150033.

2.•• Fok JS, Smith WB. Hypersensitivity reactions to gadolinium-based contrast agents. Curr Opin Allergy Clin Immunol. 2017. https://doi.org/10.1097/ACI.0000000000000371.

This study establishs the prevalence of adverse reactions to GBCA.

3. Bruder O, Schneider S, Pilz G, van Rossum AC, Schwitter J, Nothnagel D, et al. Update on acute adverse reactions to gadolinium based contrast agents in cardiovascular MR. Large multi-national and multi-ethnical population experience with 37788 patients from the EuroCMR Registry. J Cardiovasc Magn Reson. 2015;17:58. https://doi.org/10.1186/s12968-015-0168-3.

4. Carr TF. Pathophysiology of immediate reactions to injectable gadolinium-based contrast agents. Top Magn Reson Imaging. 2016;25(6):265–8. https://doi.org/10.1097/RMR.0000000000000108.

5.•• Aran S, Shaqdan KW, Abujudeh HH. Adverse allergic reactions to linear ionic gadolinium-based contrast agents: experience with 194,400 injections. Clin Radiol. 2015;70(5):466–75. https://doi.org/10.1016/j.crad.2014.12.011.

The largest study in adverse reactions to GBCA.

6. Morzycki A, Bhatia A, Murphy KJ. Adverse reactions to contrast material: a Canadian update. Can Assoc Radiol J. 2017;68(2):187–93. https://doi.org/10.1016/j.carj.2016.05.006.

7.•• Fakhran S, Alhilali L, Kale H, Kanal E. Assessment of rates of acute adverse reactions to gadobenate dimeglumine: review of more than 130,000 administrations in 7.5 years. AJR Am J Roentgenol. 2015;204(4):703–6. https://doi.org/10.2214/AJR.14.13430.

A large study in adverse reactions to GBCA.

8. Costello JR, Kalb B, Martin DR. Incidence and risk factors for gadolinium-based contrast agent immediate reactions. Top Magn Reson Imaging. 2016;25(6):257–63. https://doi.org/10.1097/RMR.0000000000000109.

9.• Forbes-Amrhein MM, Dillman JR, Trout AT, Koch BL, Dickerson JM, Giordano RM, et al. Frequency and severity of acute allergic-like reactions to intravenously administered gadolinium-based contrast media in children. Investig Radiol. 2018;53(5):313–8. https://doi.org/10.1097/RLI.0000000000000444.

A review of adverse reactions in children.

10. Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Frequency and severity of acute allergic-like reactions to gadolinium-containing i.v. contrast media in children and adults. AJR Am J Roentgenol. 2007;189(6):1533–8. https://doi.org/10.2214/AJR.07.2554.

11. Davenport MS, Dillman JR, Cohan RH, Hussain HK, Khalatbari S, McHugh JB, et al. Effect of abrupt substitution of gadobenate dimeglumine for gadopentetate dimeglumine on rate of allergic-like reactions. Radiology. 2013;266(3):773–82. https://doi.org/10.1148/radiol.12120253.
12. Murphy KJ, Brunberg JA, Cohan RH. Adverse reactions to gadolinium contrast media: a review of 36 cases. AJR Am J Roentgenol. 1996;167(4):847–9. https://doi.org/10.2214/ajr.167.4.8819369.
13. Heshmatzadeh Behzadi A, Prince MR. Preventing allergic reactions to gadolinium-based contrast agents. Top Magn Reson Imaging. 2016;25(6):275–9. https://doi.org/10.1097/RMR.0000000000000106.
14. Power S, Talbot N, Kucharczyk W, Mandell DM. Allergic- like reactions to the MR imaging contrast agente gabodutrol: a prospective study of 32991 consecutive injections. Radiology. 2016. https://doi.org/10.1148/radiol.2016151066.
15. Jingu A, Fukuda J, Taketomi-Takahashi A, Tsushima Y. Breakthrough reactions of iodinated and gadolinium contrast media after oral steroid premedication protocol. BMC Med Imaging. 2014;14:34. https://doi.org/10.1186/1471-2342-14-34.
16.• Dillman JR, Trout AT, Davenport MS. Allergic-like contrast media reaction management in children. Pediatr Radiol. 2018;48(12):1688–94. https://doi.org/10.1007/s00247-018-4241-6.

A review of adverse reactions in children.

17.• Rosado Ingelmo A, Doña Diaz I, Cabañas Moreno R, Moya Quesada MC, García-Avilés C, García Nuñez I, et al. Clinical practice guidelines for diagnosis and management of hypersensitivity reactions to contrast media. J Investig Allergol Clin Immunol. 2016;26:144–55. https://doi.org/10.18176/jiaci.0058.

It is important to assess future recommendations in patients with a previous adverse reaction.

18. Prieto-García A, Pérez-David E, Devesa C, Tornero P, Schwartz LB, Pascual C, et al. Fatal anaphylaxis caused by gadolinium due to beta-tryptase-induced hemorragic diathesis. J Allergy Clin Immunol Pract. 2017;5(5):1433–4. https://doi.org/10.1016/j.jaip.2017.05.008.
19. Granata V, Cascella M, Fusco R, dell'Aprovitola N, Catalano O, Filice S, et al. immediate adverse reactions to gadolinium-based MR contrast media: a retrospective analysis on 10,608 examinations. Biomed Res Int. 2016;2016:3918292. https://doi.org/10.1155/2016/3918292.
20. Bhatti ZS, Mervak BM, Dillman JR, Davenport MS. Breakthrough reactions to gadobenate dimeglumine. Investig Radiol. 2018;53(9):551–4. https://doi.org/10.1097/RLI.0000000000000452.
21. Xiao YD, Paudel R, Liu J, Ma C, Zhang ZS, Zhou SK. MRI contrast agents: Classification and application (review). Int J Mol Med. 2016;38:1319–26. https://doi.org/10.3892/ijmm.2016.2744.
22. Carrasco Muñoz S, Calles Blanco C, Marcin J, Fernández Álvarez C, Lafuente Martínez J. Gadolinium-based contrast agents for magnetic resonance imaging. Radiología. 2014;56(S1):21–8. https://doi.org/10.1016/j.rx.2014.06.005.
23. Pourmand A, Guida K, Abdallah A, Taheri MR, Shokoohi H. Gadolinium-based contrast agent anaphylaxis, a unique presentation of acute abdominal pain. Am J Emerg Med. 2016;34(8):1737. e1–2. https://doi.org/10.1016/j.ajem.2015.12.063.
24. Geraldesa C, Laurent S. Classification and basic properties of contrast agents for magnetic resonance imaging, contrast media. Mol Imaging. 2009;4:1–23. https://doi.org/10.1002/cmmi.265.
25.• Yoon SH, Lee SY, Kang HR, Kim JY, Hahn S, Park CM, et al. Skin tests in patients with hypersensitivity reaction to iodinated contrast media: a meta-analysis. Allergy. 2015;70(6):625–37. https://doi.org/10.1111/all.12589.

It is important to assess future recommendations based on allergy study.

26. Jung JW, Kang HR, Kim MH, Lee W, Min KU, Han MH, et al. Immediate hypersensitivity reaction to gadolinium-based MR contrast media. Radiology. 2012;264:414–22. https://doi.org/10.1148/radiol.12112025.
27. Nelson KL, Gifford LM, Lauber-Huber C, Gross CA, Lasser TA. Clinical safety of gadopentate dimeglumine. Radiology. 1995;196:439–43. https://doi.org/10.1148/radiology.196.2.7617858.
28.•• Behzadi AH, Zhao Y, Farooq Z, Prince MR. Immediate allergic reactions to gadolinium-based contrast agents: a systematic review and meta-analysis. Radiology. 2018;286(2):471–82. https://doi.org/10.1148/radiol.2017162740

It is a recent meta-analysis.

29. Batthi ZS, Mervak BM, Dillman JD, Davenport MS. Breakthrough reactions to gadobenate dimeglumine. Investig Radiol. 2018;00:N00. https://doi.org/10.1097/RLI.0000000000000452.
30. ACR manual on contrast media, version 10.3. 2018. American College of Radiology. https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed September 25, 2019.
31. Li A, Wong CS, Wong MK, Lee CM, Au Yeung MC. Acute adverse reactions to magnetic resonance contrast media–gadolinium chelates. Br J Radiol. 2006;79(941):368–71. https://doi.org/10.1259/bjr/88469693.
32. Brockow K, Sánchez-Borges M. Hypersensitivity to contrast media and dyes. Immunol Allergy Clin N Am. 2014;34:547–64. https://doi.org/10.1016/j.iac.2014.04.002.
33. Tanaka H, Urushima M, Hirano S, Takenaga M. An acute adverse reaction with ST elevation induced by magnetic resonance contrast media: A case of kounis sindrome. Intern Med. 2019;58(2):243–5. https://doi.org/10.2169/internalmedicine.0802-18.

34. Zlojtro M, Roginic S, Nikolic-Heitzler V, Babic Z, Kaliterna DM, Marinko A. Kounis syndrome: simultaneous occurrence of an allergic reaction and myocardial ischemia in a 46 year old patient after administration of contrast agent. Isr Med Assoc J. 2013;15(11):725–6.
35. Virtos M, Ruiz S, Mokrane FZ, Rousseau H, Georges B, Fourcade O, et al. Anaphylactic reaction and cardiac arrest due to gadobenate dimeglumine. Anaesth Crit Care Pain Med. 2015;34(4):247–8. https://doi.org/10.1016/j.accpm.2015.03.006.
36. Prince MR, Zhang H, Zou Z, Staron RB, Brill PW. Incidence of immediate gadolinium contrast media reactions. AJR Am J Roentgenol. 2011;196(2):W138–43. https://doi.org/10.2214/AJR.10.4885.
37. Franckenberg S, Berger F, Schaerli S, Ampanozi G, Thali M. Fatal anaphylactic reaction to intravenous gadobutrol, a gadolinium-based MRI contrast agent. Radiol Case Rep. 2017;13(1):299–30. https://doi.org/10.1016/j.radcr.2017.09.012.
38. Javaloyes G, Goikoetxea MJ, Sanz ML, Cabrera-Freitag P, Gastaminza G. Basophil activation test in the diagnosis of gadobutrol anaphylaxis. Ann Allergy Asthma Immunol. 2012;108:280–7. https://doi.org/10.1016/j.anai.2012.02.003.
39. Hasdenteufel F, Luyasu S, Renaudin JM, Paquay JL, Carbutti G, Beaudouin E, et al. Anaphylactic shock after first exposure to gadoterate meglumine: two case reports documented by positive allergy assessment. J Allergy Clin Immunol. 2008;121:527–8. https://doi.org/10.1016/j.jaci.2007.08.027.
40. Beaudouin E, Kanny G, Blanloeil Y, Guilloux L, Renaudin JM, Moneret-Vautrin DA. Anaphylactic shock induced by gadoterate meglumine (DOTAREM). Eur Ann Allergy Clin Immunol. 2003;35:382–5.
41. Kun T, Jakubowski L. Influence of MRI contrast media on histamine release from mast cells. Pol J Radiol. 2012;77:19–24. https://doi.org/10.12659/pjr.883370.
42. Tomás M, Fuentes Aparicio V, Zapatero Remon L, Alonso Lebrero E, Infante HS. Skin reactions to gadolinium-based contrast media. J Investig Allergol Clin Immunol. 2012;22:292–3.
43. Moulin C, Said BB, Berard F. Tolerability of gadobenate dimeglumine in a patient with reported allergy to gadoterate meglumine. AJR Am J Roentgenol. 2011;197:W1163. https://doi.org/10.2214/AJR.10.4372.
44. Galera C, Pur Ozygit L, Cavigioli S, Bousquet PJ, Demoly P. Gadoteridol-induced anaphylaxis - not a class allergy. Allergy. 2010;65:132–4. https://doi.org/10.1111/j.1398-9995.2009.02137.x.
45. Hasdenteufel F, Luyasu S. Anaphylactic shock after first exposure to a macrocyclic gadolinium chelate: a few comments – reply. J Allergy Clin Immunol. 2008;122:216. https://doi.org/10.1016/j.jaci.2008.05.013.
46. Boyd B, Zamora CA, Castillo M. Managing adverse reactions to contrast agents. Magn Reson Imaging Clin N Am. 2017;25:737–42. https://doi.org/10.1016/j.mric.2017.06.008.
47. Muraro A, Roberts G, Worm M, Bilo MB, Brockow K, Fernandez Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014;69:1026–45. https://doi.org/10.1111/all.12437.

Publisher's Note