Gadolinium-Based Contrast Agents: Associated Adverse Reactions

Miguel Ramalho, MD[a,*], Joana Ramalho, MD[b]

KEYWORDS

• Gadolinium-based contrast agents (GBCAs) • Adverse events • Acute allergic reactions
• Contrast media

KEY POINTS

- Immediate adverse reactions to gadolinium-based contrast agents (GBCAs) are unintended side effects occurring within 1 hour of contrast agent exposure.
- Immediate adverse reactions can be classified according to their mechanism as physiologic or hypersensitivity (allergiclike and allergic) reactions, and according to their severity, as mild, moderate, or severe.
- The most important risk factor for a GBCA reaction is previous reaction to a contrast media.
- Mild reactions may require nothing more than observation or a dose of antihistamine medication.
- Severe acute reactions need prompt treatment, because most patients recover if treated quickly and appropriately.

INTRODUCTION

All diagnostic radiological practice involves a balancing of the estimated risk of an investigation versus the perceived benefits of the information to be gained from it.[1] Overall, all available contrast materials are well tolerated and safe. However, adverse events and hypersensitivity reactions do still occur in a small percentage of patients.

Gadolinium-based contrast agents (GBCAs) have been used in Magnetic Resonance (MR) imaging since the late 1980s. These agents shorten the T1 relaxation times of surrounding water protons, resulting in marked increase of signal on T1-weighted images. This enhancement is critical in the detection and characterization of several disease processes. Therefore, GBCAs have become an indispensable part of clinical studies of the neural system, vascular system, and for body applications, being routinely used in many MR protocols, with more than 300 million doses administered worldwide to date.[2,3]

Several types and classes of GBCAs have been developed for clinical use. After almost 30 years of use, these agents have shown an excellent safety profile, being well tolerated and having a very low incidence of adverse reactions, with reports varying from 0.01% to 2.4%.[4–8] Overall, this is lower than the incidence of acute adverse reactions associated with low-osmolar nonionic iodinated contrast media used for computed tomography (CT) scans, which is already low (0.2%).[9] Severe acute reactions are extremely rare, with mortalities ranging from 0.00008% to 0.0019%.[6,10]

This article discusses GBCAs acute adverse reactions, including pathophysiologic mechanisms, incidence, symptoms, risk factors, treatment strategies, premedication, and the potential use of skin testing.

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[a] Department of Radiology, Hospital Garcia de Orta, Avenida Torrado da Silva, 2805-267 Almada, Portugal;
[b] Department of Neuroradiology, Centro Hospitalar de Lisboa Central, Rua José António Serrano, 1150-199 Lisboa, Portugal
* Corresponding author. Avenida Torrado da Silva, 2805-267 Almada, Portugal.
E-mail address: Miguel-Ramalho@netcabo.pt

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GADOLINIUM-BASED CONTRAST AGENT ADMINISTRATION RISKS

GBCA administration carries risks, including nephrogenic systemic fibrosis, gadolinium dechelation and retention in human tissue, and injection site complications, such as extravasation. Interference with laboratory tests has been described, such as pseudohypocalcemia, but these confounding effects have been largely eliminated by improvements to laboratory testing methods and protocols.[11]

GBCA subcutaneous extravasations are rare. The incidence is lower and symptoms are less severe compared with the iodinated contrast agents used for contrast-enhanced CT scans.[12] Prince and colleagues[10] reported 46 infiltrations in a total of 158,796 gadolinium-based contrast agent–enhanced examinations (3 per 10,000 administrations). Extravasation may be asymptomatic or present with itching, local swelling, and local erythema at the injection site, which resolve spontaneously or with conservative management.[12] Nevertheless, soft tissue edema, inflammation, and necrosis[10,13] may occur. Tissue damage and necrosis are extremely uncommon after GBCA extravasation, probably mainly reflecting the low volumes of GBCAs that are administered; however, when tissue damage occurs, it tends to be more advanced with agents with higher osmolality.[12,14]

ADVERSE DRUG REACTIONS: DEFINITION, CLASSIFICATION, AND PATHOPHYSIOLOGIC MECHANISM

Adverse drug reactions are defined as all unintended pharmacologic effects of a drug, excluding therapeutic failures and misadministration.[15,16] These reactions may be broadly classified as predictable or unpredictable. Predictable reactions are related to the identified pharmacologic effects of a drug, which are generally dose dependent and occur in otherwise normal patients. These effects include side effects, drug overdose, secondary effects, and interactions with other drugs. Unpredictable drug reactions are unrelated to the pharmacologic actions of a drug, may be dose independent, and may be more frequent in individuals with specific susceptibility.[17]

Unpredictable drug reactions or hypersensitivity reactions include allergic and nonallergic or allergiclike reactions. By definition, an allergic reaction refers to an antigen-specific, immunologically mediated hypersensitivity reaction to a drug in a susceptible individual. Allergic reactions are subdivided into at least 4 types according to the Coombs-Gell classification. From those 4 types, immediate allergic reactions (type 1) are immunologic reactions in which the primary feature is immunoglobulin (Ig) E mediated. In contrast, nonallergic or allergiclike reactions are caused by release of mediators from mast cells or basophils through non–IgE-mediated mechanisms.[17] Non–IgE-mediated mechanisms include direct membrane effect, complement activation, and bradykinin generation.[14] Direct effects on the basophil or mast cell membrane are related either to the chemical structure or the osmolality of the contrast material. The anaphylatoxins C3a and C4a complexes produced through the activation of the complement cascade can also activate mast cells. In patients with severe immediate reactions, increased levels of C3a and C4a have been identified. These anaphylatoxins can bind to the non-IgE receptors on the mast cell surface and lead to degranulation.[14,17,18] The non–IgE-mediated mechanism has been regarded as the primary player in immediate reactions to contrast media. However, it is unclear to what extent each non–IgE-mediated mechanism contributes to GBCA reactions, and the full range of cell types and chemicals involved.

GADOLINIUM-BASED CONTRAST AGENTS ADVERSE REACTIONS

Immediate adverse reactions are defined as unintended side effects occurring within 1 hour of contrast agent exposure. Although more delayed reactions may occur, most anaphylactic reactions develop within 20 minutes after intravenous injection of the contrast agent.

Nonimmediate adverse reactions are reactions occurring 1 hour to 10 days after injection. To our knowledge, nonimmediate hypersensitivity reactions to gadolinium chelates have not been definitively described to date, although the possibility of such a reaction occurring cannot be ruled out[19] and our opinion is that nephrogenic systemic fibrosis (NSF) and the entity gadolinium deposition disease (GDD) may fit into this category. A detailed description and discussion of either NSF or GDD is beyond the scope of this article. Only acute adverse reactions are discussed here.

ACUTE ADVERSE REACTIONS

Definition and Incidence

Classification of the contrast media adverse reactions is still controversial, mainly because the exact underlying pathophysiologic mechanism is not completely elucidated.