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Overview, Perspectives and Applications of Magnetic Resonance Imaging Contrast Agents

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Abstract

Magnetic resonance imaging (MRI) is a non-invasive clinical imaging modality, which has become widely used in the diagnosis and/or staging of human diseases around the world. Some MRI examinations include the use of contrast agents. The categorizations of currently available contrast agents have been described according to their effect on the image, magnetic behavior and biodistribution in the body, respectively. In this field, superparamagnetic iron oxide particles and soluble paramagnetic metal chelates are two main classes of contrast agents for MRI. This review outlines the research and development of MRI contrast agents. In future, the ideal MRI contrast agent will be focused on the neutral tissue- or organ-targeting materials with high relaxivity and specificity, low toxicity and side effects, suitable long intravascular duration and excretion time, high contrast enhancement with low dose *in vivo*, and with minimal cost.

Introduction

MRI contrast agents are contrast agents used to improve the visibility of internal body structures in magnetic resonance imaging (MRI).[1] The most commonly used compounds for contrast enhancement are gadolinium-based. Such MRI contrast agents shorten the relaxation times of nuclei within body tissues following oral or intravenous administration. Magnetic resonance imaging (MRI) contrast agents are categorised according to the following specific features: chemical composition including the presence or absence of metal atoms, route of administration, magnetic properties, effect on the magnetic resonance image, biodistribution and imaging applications.

MRI contrast agents have become an indispensable part of modern magnetic resonance imaging. Although MRI was initially hoped to provide a means of making definitive diagnoses non-invasively, it has been found that the addition of contrast agents in many cases improves sensitivity and/or specificity. MRI contrast agents have become an indispensable part of modern magnetic resonance imaging. Although MRI was initially hoped to provide a means of making definitive diagnoses non-invasively, it has been found that the addition of contrast agents in many cases improves sensitivity and/or specificity.

MRI contrast agents work primarily by altering the intrinsic T1 relaxation times of various soft tissues where contrast accumulates. In the hepatobiliary system, MRI contrast agentscan improve the detection of liver lesions and improve the characterization of focal liver abnormalities. MRI contrast agentsfor hepatobiliary imaging are divided into two basic categories: extracellular fluid contrast (ECF) agents, and those with additional hepatobiliary excretion. In the past, the most commonly used contrast agents were the ECF agents, such as gadopentetate dimeglumine (gadolinium diethylenetriaminepentaacetic acid [Gd-DTPA]), which is distributed within the intravascular compartment initially and rapidly diffuses through the extravascular space, similar to the action of iodinated contrast agents in computed tomography

Types

Most clinically used MRI contrast agents work by shortening the T1 relaxation time of protons inside tissues via interactions with the nearby contrast agent. Thermally driven motion of the strongly paramagnetic metal ions in the contrast agent generates the oscillating magnetic fields that provide the relaxation mechanisms that enhance the rate of decay of the induced polarization. The systematic sampling of this polarization over the spatial region of the tissue being examined forms the basis for construction of the image. MRI contrast agents may be administered by injection into the blood stream or orally, depending on the subject of interest. Oral administration is well suited to G.I. tract scans, while intravascular administration proves more useful for most other scans. A variety of agents of both types enhances scans routinely.

MRI contrast agents can be classified in many ways,[2] including by their:

1. chemical composition
2. administration route
3. magnetic properties
4. effect on the image
5. presence and nature of metal atoms
6. biodistribution and applications:
    1. Extracellular fluid agents (also known as intravenous contrast agents)
    2. Blood pool agents (also known as intravascular contrast agents)

3. Organ specific agents (i.e. gastrointestinal contrast agents and hepatobiliary contrast agents)
4. Active targeting/cell labeling agents (i.e. tumor-specific agents)
5. Responsive (also known as smart or bioactivated) agents
6. pH-sensitive agents

Contrast agents

Contrast agents can be grouped in many different ways. One way is to consider them according to the compartments in which they distribute.

- gastrointestinal MRI contrast agents
- intravenous MRI contrast agents
- intravascular (blood pool) MRI contrast agents
- tumour-specific MRI contrast agents
- hepatobiliary MRI contrast agents
- reticuloendothelial MRI contrast agents
- MRI contrast agent safety

What are contrast materials and how do they work?

Contrast materials, also called contrast agents or contrast media, are used to improve pictures of the inside of the body produced by x-rays, computed tomography (CT), magnetic resonance (MR) imaging, and ultrasound. Often, contrast materials allow the radiologist to distinguish normal from abnormal conditions.

Contrast materials are not dyes that permanently discolor internal organs. They are substances that temporarily change the way x-rays or other imaging tools interact with the body.When introduced into the body prior to an imaging exam, contrast materials make certain structures or tissues in the body appear different on the images than they would if no contrast material had been administered. Contrast materials help distinguish or "contrast" selected areas of the body from surrounding tissue. By improving the visibility of specific organs, blood vessels or tissues, contrast materials help physicians diagnose medical conditions.

Contrast materials enter the body in one of three ways. They can be:

- swallowed (taken by mouth or orally)
- administered by enema (given rectally)
- injected into a blood vessel (vein or artery; also called given intravenously or intra-arterially)

Following an imaging exam with contrast material, the material is absorbed by the body or eliminated through urine or bowel movements.

There are several types of contrast materials:

- Iodine-based and barium-sulfate compounds are used in x-ray and computed tomography (CT) imaging exams.

Contrast materials can have a chemical structure that includes iodine, a naturally occurring chemical element. These contrast materials can be injected into veins or arteries, within the disks or the fluid spaces of the spine, and into other body cavities.

Barium-sulfate is the most common contrast material taken by mouth, or orally. It is also used rectally and is available in several forms, including:

- powder, which is mixed with water before administration
- liquid
- paste
- tablet

When iodine-based and barium-sulfate contrast materials are present in a specific area of the body, they block or limit the ability of x-rays to pass through. As a result, blood vessels, organs and other body tissue that temporarily contain iodine-based or barium compounds change their appearance on x-ray or CT images.

- Gadolinium is the key component of the contrast material most often used in magnetic resonance (MR) exams. When this substance is present in the body, it alters the magnetic properties of nearby water molecules, which enhances the quality of MR images.
- Saline (salt water) and air are also used as contrast materials in imaging exams. Microbubbles and microspheres have been administered for ultrasound imaging exams, particularly exams of the heart.

What is gadolinium contrast medium?

Gadolinium contrast media (sometimes called a MRI contrast media, agents or ‘dyes’) are chemical substances used in magnetic resonance imaging (MRI) scans. When injected into the body, gadolinium contrast medium enhances and improves the quality of the MRI images (or pictures). This allows the radiologist (a specialist doctor trained to examine the images and provide a written report to your doctor or specialist) to more accurately report on how your body is working and whether there is any disease or abnormality present.

Gadolinium contrast media consist of complex molecules, arrangements of atoms held together by chemical bonds. The chemical bonds are made between a gadolinium ion and a carrier molecule (a chelating agent). A chelating agent prevents the toxicity of gadolinium while maintaining its contrast properties. Different brands of gadolinium contrast medium use different chelating molecules. The contrast medium is injected intravenously (into a vein) as part of an MRI scan, and eliminated from the body through the kidneys.

Why do I need to have gadolinium contrast medium?

Gadolinium contrast medium is used in about 1 in 3 of MRI scans to improve the clarity of the images or pictures of your body's internal structures. This improves the diagnostic accuracy of the MRI scan. For example, it improves the visibility of inflammation, tumours, blood vessels and, for some organs, blood supply.

Before the scan begins, the radiologist (specialist doctor supervising the scan) will decide, on the basis of the notes sent by your referring doctor, whether gadolinium injection is likely to be helpful and should be recommended for your MRI.

Before any MRI scan, you will be asked a number of questions about your medical history, and any implants you might have, to make sure that you will not be at risk from the strong magnetic fields of the scanner. You will also be asked about conditions that might mean a gadolinium injection would not be recommended (e.g. pregnancy, previous allergic reaction, severe kidney disease). If you have any of these conditions, then you will not be given gadolinium, but if there is no condition preventing injection, you might be asked to sign a consent form in case gadolinium is required.

Usually, you will be advised by the technologist or nurse before you have the MRI scan that it is recommended that gadolinium contrast medium be injected during the examination. As with any medical procedure, you have the right to seek further advice and/or to decline a gadolinium injection. The technologist who carries out the MRI scan, a nurse or a radiologist will give you the injection.

Sometimes, even though gadolinium initially would not have been required based on the referral notes provided by your doctor, the radiologist might decide during your scan that gadolinium would help make the images clearer. If you are told part of the way through your scan that gadolinium will be needed, you should not be concerned that this indicates something serious is wrong. Most often, this is being done to make the images clearer and of a higher quality, so the radiologist can provide your doctor with a more accurate diagnosis of your symptom or condition. If the gadolinium is not given after such a recommendation, another scan may be required later.

How is gadolinium contrast medium given to me?

Gadolinium contrast medium is given by intravenous injection, that is, through a small needle into a vein in your arm, either by hand injection or by an automated injector.

Will I feel anything when I have a gadolinium contrast medium injection?

Most patients do not notice any sensations, although a few patients will report a cold feeling in the arm during the injection, which is of no significance. An even smaller number (between about 1 and 4 in 100) will notice mild nausea or headache. Vomiting can occur, but this is rare (less than 1 in 100 injections).

How long does a gadolinium contrast medium injection take?

The injection takes between 10 and 30 seconds. If there is going to be any immediate reaction (such as those mentioned above), it will almost always be apparent within a few minutes; that is, before the end of the scan.

What are the risks of gadolinium contrast medium injections?

Gadolinium contrast medium is generally very safe. Side effects or reactions are uncommon, but can occur.

In patients with normal kidney function, most of the gadolinium contrast medium injected (over 90%) is passed out in the urine within 24 hours.

Transient reactions

The most common adverse reactions are minimal: headache, nausea (feeling slightly sick) and dizziness for a brief time after the injection. A few patients will have a feeling of coldness at the injection site.

Allergy-like reactions

Less often, in approximately 1 in 1000 patients, an itchy skin rash might appear a few minutes after the injection. This appears to be due to a mild allergy. It usually settles down by itself within an hour or so, but rarely it might be a warning sign of a more serious allergic reaction developing.

Severe allergic (anaphylactic) reactions to gadolinium contrast medium have occurred, but are extremely rare. These severe reactions, which might involve difficulty breathing and swelling of the lips and mouth, occur in approximately 1 in every 10,000 people who have gadolinium. These severe reactions generally respond very well to standard emergency drug treatment, similar to that given for other severe allergic reactions. These are usually medications that will be given through the tube that was placed in your arm before or during the MRI scan. All radiology facilities where gadolinium injections are given maintain stock of the medications required to treat these reactions, and are equipped to administer them when needed.

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis (NSF) is a rare debilitating disease resulting in skin contractures (or localised skin thickening and tightening) and internal organ damage. It has occurred with some gadolinium-based contrast media in a minority of patients with pre-existing severe kidney function abnormalities. There are some forms of gadolinium contrast for which there seem to be lower risks of NSF than for others, and these low-risk forms are used in patients with less severe renal disease if the likely benefit (better diagnosis) justifies the very low likelihood of subsequent NSF. Even in those with end-stage kidney disease, the risk of NSF developing after a single injection of a lower risk agent is believed to be well under 1 in 100 injections.

For this reason, you will be asked questions about possible kidney disease as part of the safety screening before the MRI scan. If you have kidney disease, please advise your referring doctor before the procedure, so that you, your doctor and the MRI radiologist can discuss whether or not the possible benefits of a gadolinium injection outweigh the possible risks in your case.

Gadolinium retention

Recently, it has been recognised that very small amounts of at least some forms of gadolinium contrast (about 1% of the injected dose) are retained in the tissues, mostly in the bones, with tiny amounts in the brain. This seems to be more likely with the same forms of gadolinium contrast that have a higher risk for NSF. At this stage, there are no known adverse effects from these very small amounts of retained gadolinium. This finding has made radiologists more careful to recommend gadolinium contrast only where it is likely to assist the diagnosis.

Pregnancy, possible pregnancy and lactation

If you are pregnant, or think you might be pregnant, please inform your doctor or radiologist before having the procedure, so that your doctor can consider and talk to you about any risks and benefits of having an MRI scan, and a possible gadolinium injection, for you and your unborn baby. Where relevant, you will be asked about the possibility of pregnancy as part of the safety screening before any MRI scan. If you are pregnant or possibly pregnant, it is unlikely that you will have a gadolinium injection unless it is absolutely essential. If an injection is recommended, this would be discussed with you and your doctor before giving you the injection.

If you are breast-feeding, it is safe to continue normal breast-feeding after the gadolinium contrast medium has been given. There is no requirement to express and dispose of breast milk or to withhold breast-feeding. Although the gadolinium is eliminated from the body through the kidneys, if you are breast-feeding, it has been shown that a tiny part (less than 1 part in 1000) of the injected gadolinium can enter the breast milk. An even smaller amount of gadolinium from the breast milk might be swallowed by the baby and taken into the baby's bloodstream. The amount received by your baby is so small it is not thought to represent any danger to your child.

Further questions about adverse effects?

If you have any concerns about the use of gadolinium, please discuss these with your referring doctor and/or the staff where you are having this procedure.

What are the benefits of gadolinium contrast medium injections?

Gadolinium MRI contrast injections improve diagnostic accuracy in some conditions, such as inflammatory and infectious diseases of the brain, spine, soft tissues and bones, by making images clearer so that the radiologist can better see what and where the problem is. The nature and extent of some cancers and benign tumours is best seen and assessed after a gadolinium contrast injection.

Scans showing the function of blood vessels in real time can be carried out using gadolinium contrast medium, and many heart abnormalities can only be fully assessed using gadolinium contrast medium.

Who will give me the gadolinium contrast medium injection?

If a gadolinium injection is required, it will most likely be given by a radiographer or nurse, either by hand injection through a syringe and needle, or occasionally by a mechanical injector connected to the syringe (this allows more precise timing and a more controlled rate of injection).

Where is a gadolinium contrast medium injection done?

Normally, after some initial MRI scans have been carried out, the gadolinium injection will be given to you while you are in the scanner, before more scans are taken.

If a gadolinium angiogram is carried out, some preliminary scans might be required immediately before the gadolinium injection, and it is important to lie still between the preliminary scan and the gadolinium injection.

Benefits

An MRI scanner can be used to take images of any part of the body (e.g., head, joints, abdomen, legs, etc.), in any imaging direction. MRI provides better soft tissue contrast than CT and can differentiate better between fat, water, muscle, and other soft tissue than CT (CT is usually better at imaging bones). These images provide information to physicians and can be useful in diagnosing a wide variety of diseases and conditions.

Risks

MR images are made without using any ionizing radiation, so patients are not exposed to the harmful effects of ionizing radiation. But while there are no known health hazards from temporary exposure to the MR environment, the MR environment involves a strong, static magnetic field, a magnetic field that changes with time (pulsed gradient field), and radiofrequency energy, each of which carry specific safety concerns:

- The strong, static magnetic field will attract magnetic objects (from small items such as keys and cell phones, to large, heavy items such as oxygen tanks and floor buffers) and may cause damage to the scanner or injury to the patient or medical professionals if those objects become projectiles. Careful screening of people and objects entering the MR environment is critical to ensure nothing enters the magnet area that may become a projectile.
- The magnetic fields that change with time create loud knocking noises which may harm hearing if adequate ear protection is not used. They may also cause peripheral muscle or nerve stimulation that may feel like a twitching sensation.

Materials and methods

All gadolinium-based contrast agent adverse events reported to radiology quality assurance committees were graded according to American College of Radiology criteria and divided by the total number of injections to determine incidence during the past 10 years. For each event, an age- and examination-matched control patient was identified to compare sex, weight, creatinine, eosinophil count, allergic history and gadolinium-based contrast agent dose differences. The U.S. Food and Drug Administration

(FDA) Adverse Event Reporting System (AERS) database was analyzed to compare local experience to national trends.

Conclusion

This limited retrospective analysis shows that gadolinium-based contrast agents are very safe, with only rare reports of death, and raises the possibility that nonionic linear gadolinium-based contrast agents and gadopentetate dimeglumine may have fewer severe immediate adverse events compared with gadobenate dimeglumine.

References

1. Geraldes, Carlos F. G. C.; Laurent, Sophie (2009). "Classification and basic properties of contrast agents for magnetic resonance imaging". Contrast Media & Molecular Imaging. 4 (1): 1–23. doi:10.1002/cmmi.265.
2. Lentschig, MG; Reimer, P; Rausch-Lentschig, UL; Allkemper, T; Oelerich, M; Laub, G (1998). "Breath-hold gadolinium-enhanced MR angiography of the major vessels at 1.0 T: Dose-response findings and angiographic correlation". Radiology. 208 (2): 353–7. doi:10.1148/radiology.208.2.9680558.
3. Garcia-Bournissen F, Shrim A, Koren G (2006). "Safety of gadolinium during pregnancy". Can Fam Physician. 52: 309–10.
4. Murphy KJ, Brunberg JA, Cohan RH; Brunberg; Cohan (1 October 1996). "Adverse reactions to gadolinium contrast media: A review of 36 cases". AJR Am J Roentgenol. 167 (4): 847–9.
5. Penfield, Jeffrey G; Reilly, Robert F (2007). "What nephrologists need to know about gadolinium". Nature Clinical Practice Nephrology. 3 (12): 654–68.
6. Grobner, T. (2005). "Gadolinium - a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis?". Nephrology Dialysis Transplantation. 21 (4): 1104–8.
7. Marckmann, P.; Skov, L; Rossen, K; Dupont, A; Damholt, MB; Heaf, JG; Thomsen, HS (2006). "Nephrogenic Systemic Fibrosis: Suspected Causative Role of Gadodiamide Used for Contrast-Enhanced Magnetic Resonance Imaging". Journal of the American Society of Nephrology. 17 (9): 2359–62.
8. Centers for Disease Control and Prevention (CDC) (2007). "Nephrogenic fibrosing dermopathy associated with exposure to gadolinium-containing contrast agents--St. Louis, Missouri, 2002-2006". MMWR. Morbidity and Mortality Weekly Report. 56 (7): 137–41.

9. Thomsen, H.S.; Morcos, S.K.; Dawson, P. (2006). "Is there a causal relation between the administration of gadolinium based contrast media and the development of nephrogenic systemic fibrosis (NSF)?". Clinical Radiology. 61 (11): 905–6.
10. Kanal, E.; Barkovich, A. J.; Bell, C.; Borgstede, J. P.; Bradley, W. G.; Froelich, J. W.; Gilk, T.; Gimbel, J. R.; et al. (2007). "ACR Guidance Document for Safe MR Practices: 2007". American Journal of Roentgenology. 188 (6): 1447–74.
11. Nakamura, Hiroshi; Ito, Naoki; Kotake, Fumio; Mizokami, Yuji; Matsuoka, Takeshi (2000). "Tumor-detecting capacity and clinical usefulness of SPIO-MRI in patients with hepatocellular carcinoma". Journal of Gastroenterology. 35 (11): 849–55.
12. Wang, Yi-Xiang J. (2011). "Superparamagnetic iron oxide based MRI contrast agents: Current status of clinical application". Quantitative Imaging in Medicine and Surgery. 1 (1): 35–40.
13. Taylor, Robert M.; Huber, Dale L.; Monson, Todd C.; Ali, Abdul-Mehdi S.; Bisoffi, Marco; Sillerud, Laurel O. (2011). "Multifunctional iron platinum stealth immunomicelles: Targeted detection of human prostate cancer cells using both fluorescence and magnetic resonance imaging". Journal of Nanoparticle Research. 13 (10): 4717–4729.
14. Harisinghani, Mukesh G.; Jhaveri, Kartik S.; Weissleder, Ralph; Schima, Wolfgang; Saini, Sanjay; Hahn, Peter F.; Mueller, Peter R. (2001). "MRI Contrast Agents for Evaluating Focal Hepatic Lesions". Clinical Radiology. 56 (9): 714–25.
15. Koretsky, Alan P.; Silva, Afonso C. (2004). "Manganese-enhanced magnetic resonance imaging (MEMRI)". NMR in Biomedicine. 17 (8): 527–31.
16. Lin, Yi-Jen; Koretsky, Alan P. (1997). "Manganese ion enhances T1-weighted MRI during brain activation: An approach to direct imaging of brain function". Magnetic Resonance in Medicine. 38 (3): 378–88.
17. Bisset, G. S.; Emery, K. H.; Meza, M. P.; Rollins, N. K.; Don, S.; Shorr, J. S. (1996). "Perflubron as a gastrointestinal MR imaging contrast agent in the pediatric population". Pediatric Radiology. 26 (6): 409–15.
18. Xue, Shenghui; Qiao, Jingjuan; Pu, Fan; Cameron, Mathew; Yang, Jenny J. (2013). "Design of a novel class of protein-based magnetic resonance imaging contrast agents for the molecular imaging of cancer biomarkers". Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 5 (2): 163–79.
19. Qiao, Jingjuan; Xue, Shenghui; Pu, Fan; White, Natalie; Liu, Zhi-Ren; Yang, Jenny J. (2014). "Molecular imaging of EGFR/HER2 cancer biomarkers by protein MRI contrast agents". J Biol Inorg Chem. 19 (2): 259–70.