MRSO Exam Prep Course

Module 11

Gadolinium Based Contrast (GBCA)

In MRI, gadolinium contrast is critical for pathology diagnosis. Gadolinium is a rare earth metal that is used to amplify favorable imaging during an MRI scan. Gadolinium is injected into our patient prior to the scanning procedure.

Gadolinium contrast has seven unpaired electrons, making it paramagnetic. Tissues that interact with gadolinium will exhibit magnetic effects due to the magnetism given by gadolinium. It is critical to recognize that with MRI, we are not imaging MRI contrast, but rather the effects of gadolinium on tissues in close proximity to it. T1 and T2 shortening will be seen with gadolinium within 3 angstroms of hydrogen. When gadolinium comes into contact with a tissue, its magnetism shortens the T1 and T2 relaxation times. This means that gadolinium-affected tissue will look brighter on T1 images and darker on T2 images.

There are several gadolinium compounds that can be utilized in MRI. Hepatobiliary gadolinium contrast, for example, is primarily excreted by the liver and hence ideal for detecting disease in the liver. Gadolinium products in blood pools will remain intravascular for a longer amount of time, allowing arterial and venous circulation to be displayed brilliantly even after a reasonably long period of time. Extracellular contrast is utilized to evaluate the central nervous system, but it may also be used to image other body areas.

Gadolinium, once injected into the body, must be removed by normal body functions. Gadolinium must be chelated before it can be eliminated from the body. This indicates that the gadolinium ion is bound to a ligand. This connection can be completed in two ways. The first chelate technique is referred to as linear. This approach covers the process by which a gadolinium ion binds to a linear ligand. The second approach is referred to as macrocyclic. The gadolinium ion is caged in this process. A ligand can also be charged (ionic). As a result, a gadolinium contrast can be either ionic or non-ionic.

Section 11.1 Short Term Effects

Gadolinium contrast has certain short-term side effects. These effects might range from non-allergic to allergic. Non-allergic gadolinium responses are also known as chemotoxic reactions. These involve the injection of contrast rather than the immunological reaction to contrast. Nausea, emesis, and headaches are examples of non-allergic responses.

Hives, sneezing, and swelling are examples of allergic responses. When the body reacts to the contrast media being injected, allergic responses ensue. The body will then manufacture histamines to improve capillary permeability. Anaphylaxis/anaphylactic responses can develop in severe settings. These can include breathing difficulties, heart problems, and even death. Patients who have previously had a response to the gadolinium contrast, past reactions to iodinated contrast, or a history of allergies or allergic respiratory illnesses are more likely to have a reaction to gadolinium contrast. Physiological responses are more examples of short-term consequences. Physiological responses include mechanisms other than the synthesis of

histamines in response to an autoimmune response. These side effects frequently cause nausea, headaches, vertigo, a metallic taste in the mouth, and pressure at the site.

Any negative effects caused by gadolinium contrast should be reported. The contrast utilized, the amount of contrast injected, the date, and the lot number should all be documented. Communication with our patients after the injection should occur in order to prevent difficulties with short-term consequences linked with contrast media.

Section 11.2 Long Term Effects

Gadolinium is linked to two categories of side effects. As previously mentioned, the first is short-term negative impacts. The second category is long-term negative effects. Each of these negative outcomes has the potential to damage our patients.

Long-term consequences of gadolinium on our patients are both known and unknown. Nephrogenic systemic fibrosis, gadolinium retention, gadolinium-associated plaques, and anthropogenic consequences are among them. There are several types of gadolinium contrast. These agents vary from non-ionic to ionic, and from linear to macrocyclic. These explain the process of attaching or chelating a gadolinium ion to a ligand. The more stable the agent, the stronger the connection.

Gadolinium contrast is classified into three types or groups. To comprehend these classifications, we must first learn specialized vocabulary. For example, the term "unconfounded" denotes when something is unequivocally established to be a cause. If the gadolinium agent is shown to be a cause of nephrogenic systemic fibrosis, it indicates that individuals who received only that gadolinium agent had nephrogenic systemic fibrosis. A confounding agent, on the other hand, would depict a patient who has received many contrast agents, yet a single agent cannot be demonstrated to have a detrimental impact. Gadolinium doses are typically measured in millimoles per kilogram. The number of millimoles per kilogram provided to our patient is referred to as the contrast agent dosage. This normally varies from 0.1 to 0.3 millimoles per kilogram.

Gadolinium agents are classified into three types. The first category of contrast agents has a weak connection and is considered unstable. This suggests that most of these chemicals are found in processes and circumstances related to transmetallation (nephrogenic systemic fibrosis).

Agents in **Group 1** include:

- Gadodiamide (Omniscan®)
- Gadopentetate dimeglumine (Magnevist®)
- Gadoversetamide (OptiMARK®)

Group 2 gadolinium agents are agents that are stable and have not been demonstrated to confound systemic fibrosis effects. Among these agents are:

- Gadobenate dimeglumine (MultiHance®)
- Gadoteridol (ProHance®)
- Gadoteric acid (Dotarem®)
- Gadobutrol (Gadavist®)

Inderal macrocyclic drugs in **Group 3** are extremely stable. These are some examples:

- Gadofosveset (Ablavar®)
- Gadoxetic acid (Eovist®)

We should also go through some extra gadolinium issues. One common misperception about MRI contrast is that it should never be administered to pregnant patients. It is suggested that pregnant patients avoid gadolinium products; nonetheless, these individuals may receive these medicines if the benefits outweigh the dangers. The ordering physician and accompanying radiologist make this decision. Gadolinium agents have been proven in studies to pass the blood-placenta barrier and reach the fetus. When needed, more stable medicines (group 2 or 3) should be administered to pregnant patients.

Furthermore, the mutagenesis effects of gadolinium-based contrast agents have not been proved to be harmful to the human fetus. Women in their first trimester of pregnancy who are administered gadolinium contrast agents exhibit no signs of teratogenesis or mutagenesis processes, according to studies. However, no sufficient or well-controlled investigations on gadolinium-based drugs and teratogenic consequences have been conducted.

Because the effects of gadolinium-based contrast on a developing fetus are uncertain, these agents should be used with caution. The attending radiologist must clarify with the referring physician that the MRI scan actually requires IV contrast to establish an appropriate diagnosis. This indicates that the knowledge gained by administering gadolinium-based contrast agents will assist both the patient and the fetus, and that waiting for the patient to give birth is not an option. It is also advised that the pregnant patient and referring physician are aware of the possible dangers and advantages of having an MRI with a gadolinium-based contrast agent.

Another factor to consider in MRI is that patients who are nursing and get a dosage of gadolinium-based contrast agents should follow particular recommendations. It was previously recommended that a patient who is nursing their child and receives a gadolinium-based contrast injection refrain from breastfeeding for 12 to 24 hours following the injection. There are no advantages to waiting more than 24 hours. When compared to the data obtained, this is considered a cautious strategy. According to new guidelines, there is no need to wait after a nursing woman receives a dose of gadolinium contrast. It has been found that the infant's stomach absorbs only a very little quantity of gadolinium-based contrast medium. When informed that their newborn may receive a minor dosage of gadolinium-based contrast, the mother must ultimately decide whether or not to discard breast milk. Any patient who is

pregnant or nursing should be administered a group 2 or group 3 agent. Macrocyclic and stable linear agents are examples of these agents.

11.2.1 Nephrogenic Systemic Fibrosis

The use of gadolinium contrast has been associated with nephrogenic systemic fibrosis (NSF). This is seen as a progressive condition. Gadolinium administration was regarded to be safe prior to this revelation. As a result, gadolinium agents were administered to patients without worry of causing injury. Individuals were given double or triple dosages of gadolinium. The relationship between gadolinium agents and nephrogenic systemic fibrosis was discovered years after researchers discovered higher zinc levels in the urine of patients who had just received gadolinium contrast.

A Glomerular Filtration Rate (GFR) has been established to prevent the long-term consequences of NSF. This takes into account a patient's weight, creatinine, gender, and age. The following list provides more information regarding GFR:

- GFR over 90 signifies normal kidney function, according to the National Kidney Foundation.
- A GFR of 60 to 90ml/min/1.73m² indicates minor decreases in renal function.
- GFRs ranging from 45 to 60 ml/min/1.73m² suggest mild to moderate renal function decline.
- GFR values ranging from 30-45 ml/min/1.73m² suggest moderate to severe renal function decline.
- GFRs ranging from 16 to 29 ml/min/1.73m² suggest serious renal disease.
- Kidney failure is indicated by a GFR of 0-15 ml/min/1.73m².
- A GFR higher than 60 ml/min/1.73m² is considered a safe threshold for the administration of contrast media to a patient. Most contrast agents enable injections of more than 30 ml/min/1.73m², and using them in individuals with GFRs less than 30 is considered off-label and not advised.

11.2.2 Transmetallation

Transmetallation is a mechanism that causes nephrogenic systemic fibrosis. This process is more likely to occur with group 1 gadolinium drugs. This implies that, except for MultiHance®, linear non-ionic agents and other linear agents are deemed unstable. As a result, if they remain in a patient's system for an extended period of time, they have a larger probability of undertaking the transmetallation process. This is the process by which a gadolinium ion splits from its ligand and takes up another element, such as zinc inside the body.

As a result, the zinc ion is eliminated from the patient's system, but the gadolinium ion remains.

With that said, we may assume that several causes contribute to this sickness. For example, increasing the dose of gadolinium agents given to our patient would increase the likelihood of transmetallation occurring. Furthermore, patients with impaired renal function may cause the gadolinium agent to linger in their system longer, increasing the likelihood of this process occurring. Finally, unstable agents raise the risk of this condition.

There have been no cases of nephrogenic systemic fibrosis in the last five years. Improved MR safety standards have helped prevent this dreadful illness from happening as a result of increasing knowledge of it. These safe practices include restricting gadolinium agent dosages to renally challenged patients, lowering the dose provided to patients, and employing gadolinium agents from groups 2 and 3.

11.2.3 Gadolinium Retention

Gadolinium deposition is a novel subject in the field of MRI safety. It is a fascinating and challenging topic to grasp. It is critical to recognize that gadolinium deposition occurs with all contrast agents. MRI tests and autopsy have shown that gadolinium agents, whether water-soluble or non-water-soluble, will persist in a patient's system. As a result, the retained gadolinium can be seen visually as T1 shortening or by analyzing tissues to determine its presence inside them.

T1 shortening on an MRI test is typically associated with gadolinium deposition. The brain is a common site of T1 shortening. Gadolinium is most commonly observed in the Globus Pallidus and Dentate Nucleus. There is no proof that this phenomenon is causing problems in our patients. However, there has been a suggestion that gadolinium accumulation might impair memory and cognitive abilities.

Gadolinium accumulation in bone is rarely studied, yet it may provide a greater danger to our patients due to the potential impacts on bone integrity and marrow within the bone. It is critical to recognize that all contrast agents exhibit some sort of gadolinium deposition. This might be observed as T1 shortening in the brain or assessed postmortem in the bone as retained gadolinium. This comprises agents that are linear or macrocyclic. T1 shortening in the brain may be accompanied by limited deposition in bone or vice versa. All linear agents are involved in a continuous discussion.

T1 shortening in the brain has been proven, and macrocyclic drugs may be too wide. T1 shortening in the brain has been seen in all group 1 agents, which are all linear agents. MultiHance, on the other hand, is a group 1 agent with probably modest T1 shortening. However, the general assertion that all linear agents exhibit T1 shortening is erroneous. This should be emphasized as linear agents may exhibit varying degrees of T1 shortening.

A few things influence gadolinium retention. According to preliminary studies, patients who received more than 77 mL of group 1 gadolinium agents showed evidence of T1 shortening in the brain. This suggests that repeated gadolinium dosages enhanced gadolinium accumulation.

The amount and location of gadolinium retention will also be determined by the type of agent utilized. Finally, gadolinium retention has been seen in individuals with normal and reduced renal function. However, preliminary findings show that renally compromised individuals may have higher levels of gadolinium deposition than those with normal kidney function.

Although the method of gadolinium retention is not fully known, it is thought that gadolinium follows similar routes as other elements such as iron and calcium. Furthermore, disorders such as multiple sclerosis have been linked to greater iron levels in brain regions such as the dentate nucleus. Because these are the sites of T1 shortening caused by repeated gadolinium injection, it is hypothesized that the same mechanisms that impact iron and calcium may also affect gadolinium ions.

11.2.4 Anthropogenic Gadolinium

The naturally available contrast among tissues in the body allows us to achieve good scans in our patients. Contrast enhancement (CE) was thought to be unnecessary in MRI at first. MRI is extremely sensitive to detecting pathologic diseases even without the addition of a contrast agent. However, as the science progresses, it is becoming obvious that adding a contrast agent to an MRI scan can significantly improve the diagnostic utility of the scan by boosting disease sensitivity and specificity, as well as defining pathologic processes.

CE is required for appropriate distinction in several parts of the body when adjacent tissues have similar MRI appearances. CE can also be used to determine the blood-brain barrier's structural integrity. Imaging of areas of normal versus decreased tissue perfusion is possible with the addition of a contrast agent.

Section 11.3 Approaches to Contrast Enhancement

The physical features of tissue (such as viscosity and temperature), as well as the chemical variables that influence:

- Proton density (PD)
- Spin-lattice relaxation (T1), and
- Spin-spin relaxation (S1)

Determine the normal MRI appearance of tissue (T2). Although modifying a sample's physical characteristics is valuable for in vitro investigations, using a sufficiently substantial alteration in a living organism to make this strategy useful in vivo is often not safe.

However, it is conceivable to safely alter the chemical features of living tissue to affect the MRI parameters and, as a result, the look of the image:

- The hydrogen content (PD)
- Spin-lattice relaxation (T1)
- Spin-spin relaxation (T2)
- Flow across the area being studied, and
- The magnetic susceptibility of the tissue

All influence the image contrast in MRI. The appearance of the MR image is altered if any of these characteristics are altered by the addition of a contrast agent. Positive CE occurs when an MRI contrast agent causes the tissue of interest to seem brighter. When a contrast agent is applied, the CE is negative if the tissue of interest is darker.

11.3.1 Altering Hydrogen Content

Changing the hydrogen content (PD) of tissue is the most evident route to CE. Water loading to raise the overall signal from the kidneys and bladder and diuretics to reduce tissue hydration are two examples of this strategy. Another option is to eliminate the source of the signal by filling the area of interest with a hydrogen-free contrast agent. The use of oxygen is another option. Unfortunately, despite the fact that oxygen is paramagnetic, the impact is too weak to be useful in therapeutic settings. The amount of MR signal generated by tissue can also be altered by adjusting the water-to-fat ratio in that tissue.

Because fat and water have very distinct relaxing properties, dramatically increasing the amount of fat can greatly increase the available signal. This method has been utilized to image the gut using fat-containing substances like mineral oil administered orally.

11.3.2 Altering the Local Magnetic Field

Motion Reduction

One way to alter the magnetic environment that spins perceive is to use a substance that drastically slows hydrogen's usual mobility. A hydrogen ion normally tumbles fast enough to average out any changes in the local magnetic environment. Local magnetic field changes become visible when the hydrogen ion is slowed. The relaxation durations, particularly T2, are shortened as a result of this. This method is restricted. However, it has been used to treat CE in the gastrointestinal tract with considerable success.

Paramagnetic/Superparamagnetic Agents

Administering a paramagnetic or superparamagnetic substance is the most versatile way to change the local magnetic environment of spins. Gadolinium, dysprosium, and manganese are the most frequent paramagnetic agents**.** Unpaired electron spins, in particular electron orbital shells of transition metals or lanthanides, provide the paramagnetic feature.

Contrast Agents Specific for Magnetic Resonance Imaging Introduction

The use of intravenous contrast media in MR has been well-established in clinical practice over the last ten years. In many cases, intravenous contrast media provide vital extra diagnostic information. The most common type of MR contrast medium is gadolinium chelates, which are believed to be quite safe. Non-ionic iodinated contrast agents are regarded to be safer than these.

There are now six intravenous MRI contrast agents that have received widespread approval and use. Gadopentetate dimeglumine, gadoteridol, gadodiamide, and gadoterate meglumine are four gadolinium chelates, one manganese chelate (mangafodipir trisodium), and one iron particle is among them (superparamagnetic iron oxide). Not all of these are available in every nation due to market size and commercial considerations.

These six contrast agents, however, are the most commonly employed in clinical practice today. The first four (the gadolinium chelates) are the most popular. The first three gadolinium agents (gadopentetate dimeglumine, gadoteridol, and gadodiamide) have the largest market share of gadolinium agents.

Image 11.1

Section 11.4 Gadolinium Chelates

11.4.1 Differentiation of the Gadolinium Chelates

The agents can be distinguished based on their:

- Osmolality – The concentration of particles dissolved in a fluid.

- Viscosity –A substance's resistance to flow.

Because they are non-ionic, gadoteridol and gadodiamide have the lowest osmolality and viscosity. Low osmolality and viscosity are major advantages of iodinated agents. In MR, where lower contrast volumes are commonly utilized, these characteristics are less important. The osmolality and viscosity of gadopentetate dimeglumine are the highest.

When injecting by hand, the difference in viscosity of the agents is readily apparent. Gadoteridol and gadodiamide can both be injected quickly and with little pressure on the plunger. When using small-diameter catheters, gadopentetate dimeglumine requires significantly more pressure to inject and is difficult to inject fast (by hand).

The stability of gadolinium chelates in vivo is a major factor in their safety. The chelates were created to attach the gadolinium ion very tightly, ensuring that the intact chelate was excreted almost completely by the kidneys. The potential release of free gadolinium in vivo is a key safety concern in the development of this class of medicines. This heavy metal is highly poisonous. Gadolinium is not a naturally occurring trace element in the body.

Gadopentetate Dimeglumine

In the late 1980s, gadopentetate dimeglumine was cleared for therapeutic usage. The current approval in the United States is only for a dose of 0.1 mmol/kg. The injection rate can't be more than 10 ml/15 s. A dosage of up to 0.3 mmol/kg can be given in Europe.

Many early clinical trials established the efficacy of this medication, as it was the first to be licensed. Enhancement, in particular, immediately became apparent as a valuable source of differential diagnostic information, allowing lesion detection among otherwise isointense masses.

Urticaria

In significantly less than 1% of individuals, the four gadolinium chelates currently in clinical use produce hives (urticaria). On this basis, it is impossible to distinguish between these four diagnostic agents. The incidence rate is taken from similar clinical trial publications as a point of reference. A "rash" (thought to be a treatment-related reaction) was observed in 0.3 percent of 1068 patients taking gadopentetate dimeglumine.

"Urticaria" (perhaps related to contrast injection) was reported in 0.2 percent of 411 individuals who received gadoteridol. Urticaria was reported in 0.7 percent of 439 individuals taking gadodiamide. Severe itching was reported in 0.4 percent of 518 patients who took gadoterate meglumine.

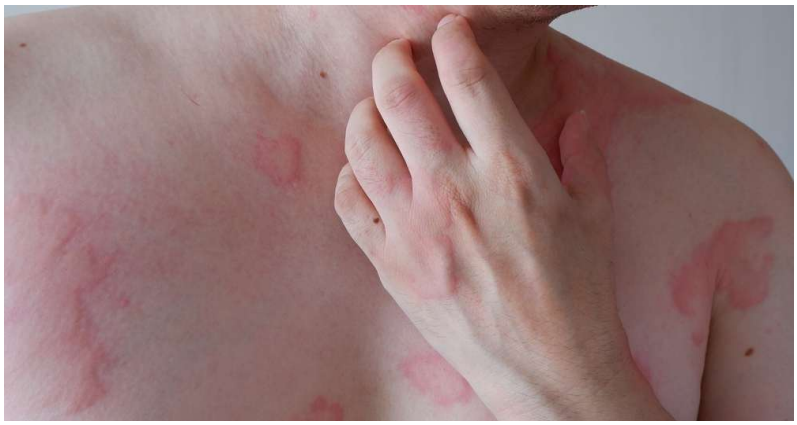


Image 11.2

Ferumoxides

Ferumoxides, which are huge superparamagnetic iron oxide particles, are employed in two different formulations all over the world. Feridex® (Ferumoxides, Berlex Laboratories) is the brand name for the substance, which contains 11.2 mg of iron per milliliter in the United States. In Europe, the identical chemical is sold as EndoremTM and is supplied at twice the concentration (Guerbet).

Approval is for the same dose, 0.56 mg of iron per kilogram of body weight, regardless of country. China, Japan, and the majority of South America also have access to the agent. The substance is a reddish-brown superparamagnetic iron oxide colloid with dextran. Following intravenous delivery, the particles are taken up by the reticuloendothelial system. The iron is then absorbed into the body's normal iron metabolism cycle.

Section 11.5 Off-Label Use of Gadolinium Chelates

Off-label use is described in diagnostic radiology as the use of an approved contrast agent in patients for a purpose not specified in the product labeling. Off-label usage is legal (and not illegal in the United States) as long as it is done in the course of normal medical practice and not as part of a safety or effectiveness study. In the United States, radiologists are permitted to utilize approved contrast media in any way that they believe is best for the patient. The FDA does not have the power to regulate this type of use.

11.5.1 Infants

In the United States, none of the gadolinium chelates are licensed for use in children under the age of two. Post-contrast scans in babies with probable neoplastic illness or current infection in

the central nervous system provide important differential diagnostic information as well as enhanced lesion detection. Despite the publication of multiple short trials, there has been no large-scale investigation of clinical safety in this patient population.

11.5.2 Dose

The use of gadolinium chelates with contrast doses larger than 0.1 mmol/kg has grown more common in recent years. Because gadopentetate dimeglumine is only approved for a dose of 0.1 mmol/kg in the United States, this is an off-label use. Although gadoteridol and gadodiamide are allowed for use up to 0.3 mmol/kg in the United States, the labeling is restricted. As a result, even when these drugs are used at large doses, such as for MR angiography or brain perfusion studies, they are deemed off-label.

11.5.3 Renal failure

Despite the lack of formal permission for this purpose, gadolinium chelates are utilized in patients with renal impairment or failure. There are numerous clinical indications. Glomerular filtration removes:

- Gadopentetate dimeglumine
- Gadoteridol
- Gadodiamide, and
- Gadoterate meglumine from the body.

All drugs should be used with caution in patients with compromised renal function, as stated in the package inserts. These four gadolinium chelates can all be dialyzed.

11.5.4 Pregnancy

All MR contrast media have been shown to have adverse effects on the fetus in animal studies, to varying degrees depending on the agent. In rats and rabbits, gadopentetate dimeglumine has been demonstrated to mildly slow fetal growth (at 2.5 times the human dose, 0.1 mmol/kg). In both animals, no congenital abnormalities were discovered.

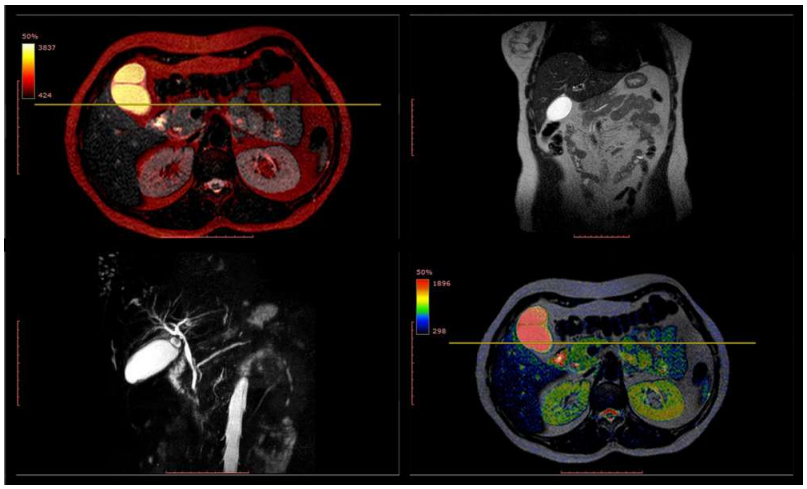


Image 11.3

11.5.5 Oral Contrast Media

In MR, opacification of the gastrointestinal tract with oral and rectal contrast can help identify normal gut from nearby tissues, whether normal or pathological. The use of oral contrast media to negate the signal from overlapping colon in MR cholangiopancreatography (MRCP) is a relatively novel application for oral contrast media.

There are two types of agents:

- Those that increase signal intensity (or positive contrast enhancement) and
- Those that reduce the signal intensity (or negative contrast enhancement).

History

The first commercial contrast agent was clinically introduced in 1988 and is the active ingredient in Magnevist. Three more contrast agents have received FDA approval for clinical MRI usage.

- Gadoterate meglumine,
- Gadoteridol, and
- Gadodiamide.

Section 11.6 Gadolinium

Gadolinium has the following general characteristics:

- Gadolinium is an atomic number 64 chemical element with the symbol Gd.
- When oxidation is eliminated from gadolinium, it becomes a silvery-white metal.
- It is a ductile rare-earth element that is just slightly bendable.
- Gadolinium forms a black covering when it interacts slowly with ambient oxygen or moisture.
- Gadolinium is ferromagnetic below its Curie point of 20 °C (68 °F), with a magnetic field attraction greater than a nickel.
- It is the most paramagnetic element above this temperature.
- It only exists in the oxidized form in nature.

11.6.1 Physical Characteristics

The eighth member of the lanthanide series is gadolinium. It is found in the periodic table between the elements europium and terbium on the left, and above the actinide curium on the right. It's a silvery-white rare-earth element that's malleable and ductile.

11.6.2 Chemical Characteristics

Gadolinium has the following chemical characteristics:

- Most elements mix with gadolinium to generate Gd (III) derivatives.
- At high temperatures, it also forms binary compounds with nitrogen, carbon, sulfur, phosphorus, boron, selenium, silicon, and arsenic.
- Metallic gadolinium, unlike the other rare-earth elements, is relatively stable in dry air.
- Gadolinium is a powerful reducing agent that breaks down metal oxides into their constituent components.
- Gadolinium is electropositive and forms gadolinium hydroxide when it interacts slowly with cold water and fast with hot water.

11.6.3 Applications

Gadolinium has a range of specialist uses but no large-scale applications. Because Gd has a large neutron cross-section, it is employed in neutron therapy to target malignancies. This element is suitable for use in neutron radiography and nuclear reactor shielding. Some nuclear reactors, notably those of the CANDU reactor type, employ it as a secondary emergency shut-down precaution.

Gadolinium is also employed as a burnable toxin in nuclear marine propulsion systems. Gadolinium has remarkable metallurgical qualities, enhancing the workability and resilience of

iron, chromium, and related alloys to high temperatures and oxidation with as little as 1% of gadolinium.

11.6.4 Additional Side Effects of Gadolinium

Gadolinium-based contrast agents have generally moderate side effects. Injection site discomfort, nausea, itching, rash, headaches, and dizziness are the most prevalent adverse effects. Depending on the brand of medicine used, people who have an MRI scan using a GBCA may suffer coolness at the injection site, changed taste, or the sensation of pins and needles.

Toxicity

Toxicity is an adverse effect of GBCA that can happen within hours after having an MRI scan with one of these contrast agents. It can also appear years later in those who have accumulated gadolinium in their systems.

Symptoms differ from one individual to the next. The severity of the condition varies from minor to severe.

- Bone or joint pain
- Skin burning or "pins and needles" sensations
- Dementia
- Headache
- Nausea
- Coldness at site
- Warmth in body
- Changes in vision or hearing
- Skin changes such as thickness and discoloration
- Vomiting, nausea, or diarrhea
- Breathing problems
- Symptoms of the flu
- Tastes metallic

Allergic Reactions

The following are signs of mild allergic reaction:

- Itching
- Readiness
- Rash
- Information

The patient's cells detect a foreign object in the body and are seeing the object as harmful. Use antihistamines in the form of pills, tablets, eye drops, nasal sprays, and creams to treat as necessary. Monitor the patient and stay in communication on how they are feeling. Hydrate frequently.

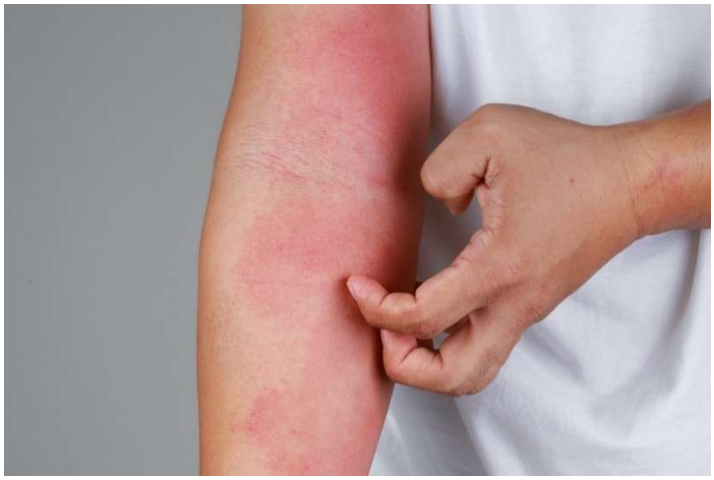


Image 11.4

The following are signs of a moderate allergic reaction:

- Hives
- Difficulty breathing
- Vigo
- Severe vomiting

Image 11.5

Similar to the mild reaction, moderate reaction should require additional monitoring and possibly medication. Monitor the patient and stay in communication frequently.

The following are signs of a severe allergic reaction:

- Cardiac arrhythmia
- Cardiac arrest
- Circulatory collapse

This reaction requires a fast response and immediate medical treatment. Medications and or antihistamines should be considered. Nurses and physicians should be brought in for treatment.

Image 11.6

Since gadolinium is toxic, it needs to be attached to something within the body in order for the body to remove it. This process is called chelation.

Section 11.7 Risks of GBCAs

11.7.1 Nephrogenic Systemic Fibrosis (NSF)

NSF is a rare disease that occurs mainly in patients with reduced kidney functions. The disease may appear on the skin, joints, eyes, and internal organs. NSF is seen in patients who are exposed to GBCAs. Some patients may receive mild effects of NSF on their skin. This results in the thickening and darkening of the skin and subcutaneous tissue.

Recent studies have linked the patient's estimated glomerular filtration rate (eGFR) produced by the kidneys and contracting NSF. EGFR is a measure of how well your kidneys filter blood over a 1-minute period of time. The higher your eGFR is, the greater the amounts of blood that are filtered through your kidneys. Studies have found that lowered levels of eGFR increase the chances of contracting NSF. To understand eGFR and kidney function, we must first understand the stages:

- Stage 1 (Normal function) – eGFR > 90/ml/min/1.73m²
- Stage 2 (Mildly decreased function) – eGFR = 60 - 90/ml/min/1.73m²

- Stage 3a (Mild to moderate function) – eGFR = 45 - 59/ml/min/1.73m²
- Stage 3b (Moderate to severe function) – eGFR = 30 - 44/ml/min/1.73m²
- Stage 4 (Severely decreased function) – eGFR = 15 - 29/ml/min/1.73m²
- Stage 5 (Kidney failure) – eGFR < 15/ml/min/1.73m²

Studies have found that patients who have an eGFR < 30 should not receive a GBCA because they have a significantly increased risk of contracting NSF.

11.7.2 People at Risk and the Causes

Because of their structure, linear GBCAs are more prone to produce toxicity than macrocyclic drugs. These are the two types of GBCAs accessible in the United States. Omniscan, a linear GBCA, produced skin lesions, skin thickening, and cell swelling in rats. The lesions were connected to elevated gadolinium levels in the skin, liver, and femur.

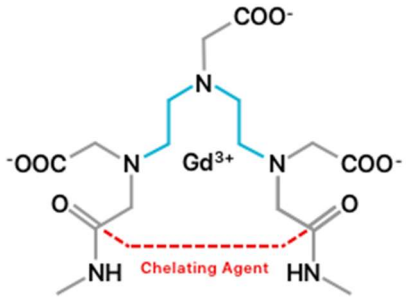
People who undergo several MRIs with GBCAs may be more susceptible to toxicity.

According to the FDA, pregnant women, those with renal difficulties, persons with inflammatory diseases, and youngsters are all at higher risk of these concerns.

11.7.3 Treatment and Testing

Few clinicians are aware of this sort of toxicity, and testing for it is difficult. Urine and blood testing are the most common tests. Normal ranges for each GBCA have yet to be established, and these techniques must be thoroughly evaluated and standardized before they can be used to monitor gadolinium levels.

Chelation is a treatment for removing hazardous quantities of heavy metals from the body. However, it hasn't been thoroughly researched as a treatment for gadolinium poisoning. Chelation is a medical procedure in which patients are given chelating chemicals. These substances bind gadolinium and eliminate it through the kidneys.



Chelating Agent

Image 11.7

Section 11.8 Bonding Structures and Contrast Stability

A gadolinium ion bonds to a molecule called a ligand. Depending on how the gadolinium is structured, the contract agent can have two different types of bonds:

- **Linear Bond**: Attaches to a gadolinium ion in a claw-like manner.
- **Macrocyclic Bond**: Attaches to a gadolinium in a cage.

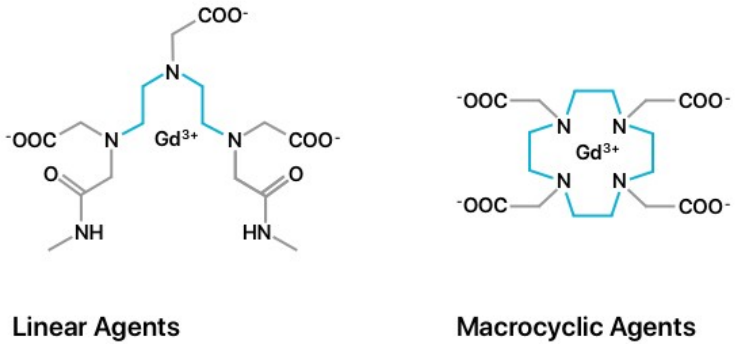


Image 11.8

The manner in which gadolinium bonds within our patient is of crucial significance because various factors within our patient's body can work to break these bonds. Linear agents are considered unstable due to their weak bonds, which makes them more vulnerable to breaking down within the body. Understanding the intricacies of gadolinium bonding is essential for ensuring the effectiveness and safety of medical procedures involving contrast agents.

11.8.1 Ionic and Non-Ionic Bonds

Ionic Bonds

Ionic describes a type of bonding that involves the electrostatic attraction between oppositely charged ions. This occurs when an atom gives one or more electrons to another atom. In the case of the sodium chloride (salt) image provided below, the transfer of electrons changed the charge of sodium to positive and chlorine to negative. Similar to a magnet, the positive and negative charges create an attraction to pull toward each other. These same bonds can occur in gadolinium and the ligand, making their bonds to be ionic. This process will greatly increase the bond between the gadolinium and the ligand.

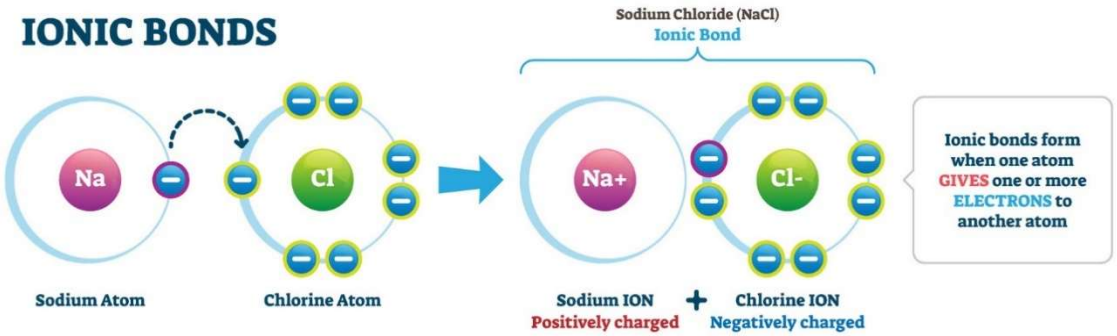


Image 11.9

Non-ionic Bonds

Contrary to ionic bonds, non-ionic bonds do not have a charge between them. Without this additional force being applied to keep the atoms together, the bond is viewed as more "unstable." Image 11.10 shows the increasing stability as we consider linear, macrocyclic, non-ionic, and ionic bonds with linear non-ionic bonds being less stable and macrocyclic ionic bonds being the most stable.

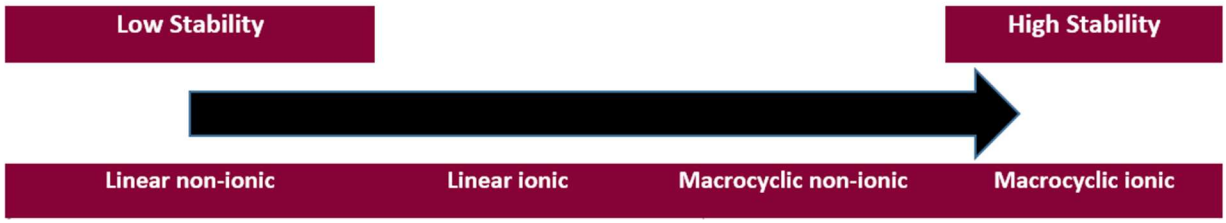


Image 11.10

11.8.2 MRI Contrast Stability

There are primarily two stability properties we need to consider when analyzing various contrast agents – kinetic stability and thermodynamic stability.

- **Kinetic Stability**: The stability of the contrast agent in our patient due to the patient's own body chemistry. This is the rate at which the gadolinium bond begins to break from its ligand due to its environment. The chemistry inside the patient's body has other elements that are fighting to bond with the gadolinium. Some of these elements within our patient's body are calcium, zinc, and iron.
- **Thermodynamic Stability**: The stability of the contrast media itself. Whereas kinetic energy focuses on the external forces that are trying to break the bond, thermodynamic stability focuses on the internal construction of the contrast media.

The kinetic stability greatly increases when the contrast is macrocyclic. The contrast kinetic stability changes from seconds to hours as the bond changes from linear to macrocyclic. Thus, the stability of a contract media is viewed as the following:

Stability of Contrast Agents			
Contrast Agent	**Structure**	**Thermodynamic Stability** Log K (therm)	**Kinetic Stability** T1/2 at pH 1.0
Dotarem® (gadoterate meglumine)	Macrocyclic ionic	25	338 hr
Gadavist® (gadobutrol)	Macrocyclic non-ionic	21.8	43 hr
ProHance® (gadoteridol)	Macrocyclic non-ionic	23.8	3.9 hr
MultiHance® (gadobenate dimeglumine)	Linear ionic	22.6	<5s
Magnevist® (gadopentetate dimeglumine)	Linear ionic	22.1	<5s
Omniscan® (gadodiamide)	Linear non-ionic	16.9	<5s
OptiMARK® (gadoversetamide)	Linear non-ionic	16.6	<5s

Table 11.1