



Magnetic Resonance Imaging Contrast Agents: A Review of Literature

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ABSTRACT

Magnetic Resonance Imaging (MRI) contrast agents most commonly agents used in diagnosing different diseases. Several agents have been ever introduced with different peculiar characteristics. They vary in potency, adverse reaction and other specification, so it is important to select the proper agent in different situations.

We conducted a systematic literature search in MEDLINE/PUBMED, Web of Science (ISI), Scopus, Google Scholar by using keywords “gadolinium” and “MRI contrast Medias”, “Gadofosvest”, “Gadobenate” and “Gadoxetate”. The most frequent contrast media agents made based on gadolinium (Gd). These are divided into two categories based on the structure of their chelating parts, linear agents and macrocyclic agents. All characteristics of contrast media factors, including efficiency, kinetic properties, stability, side effects and the rate of resolution are directly related to the structure of chelating part of that formulation.

In vitro data has shown that the macrocyclic compounds are the most stable Gd-CA as they do not bind to serum proteins, they all possess similar and relatively low relaxivity and the prevalence of Nephrogenic Systemic Fibrosis (NSF) has decreased by increasing the use of macrocyclic agents in recent years. No cases of NSF have been recorded after the administration of any of the high-relaxivity protein interacting agents, the vascular imaging agent gadofosveset trisodium (Ablavar), the hepatic imaging agent gadoxetate meglumine (Eovist), and the multipurpose agent gadobenate dimeglumine (MultiHance). In pregnancy and lactating women, stable macrocyclic agent is recommended.

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Introduction

Contrast media agents made based on gadolinium (Gd) are one of the most extensively used agents for MRI imaging. In recent years, near 40 to 50% of all MR imaging worldwide have been done by application of MRI contrast agents and a continuous rising is expected

annually (1). Gadolinium based contrast media contain gadolinium ions that belong to lanthanide groups of elements. Free gadolinium is highly toxic and may cause disturbances in normal body functioning such as: impaired function of voltage-dependent calcium channels (even with concentrations of nano-mole level), dysfunction of some enzymes, reticuloendothelial system dysfunction and increased release of inflammatory cytokines (1).

To prevent the disturbances mentioned above, in various formulations these ions are usually chelated with different

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ligands, reproducing several distinct contrast agents with various structure, efficiency and complication (2). It seems that no comprehensive review article describing contrast agents that made based on gadolinium has been published. Therefore, we decided to review the available literature regarding all characteristics and differences among different groups of Gd-CA, including the advantages and disadvantages of their physicochemical profiles. We reviewed the differences between chemical structure, side effects, efficacy and using of Gd Medias in pregnancy and lactation

Methods

A comprehensive literature search was conducted in PubMed, Web of Science (ISI), Scopus, and Google Scholar from 1966 to March 2014. The mentioned resources were searched using following terms: gadolinium and MRI contrast medias, Gadofosvest, Gadobenate, Gadoxetate in combination with one of the following phrases chemical structure, side effects, efficacy and their safety in pregnancy and lactation in appropriate resources.

Inclusion/Exclusion Criteria

We included all of the review, original, clinical trial studies on all characteristics of Gd-CA. We excluded letters, thesis, abstracts of seminars, book chapters and articles in any languages other than English.

Data Extraction

Three authors evaluated these articles regarding inclusion and exclusion criteria. Most of the considerable data of these articles were extracted in one table. We presented the name of contrast agents, approved doses, molecular structures, excess ligand, classification, osmolality, viscosity, half-life, relativity and their specificity for body region. Severity, causality and/or preventability of ADRs were also mentioned if they were pointed out in the article.

Results

Chemical structure of gadolinium containing contrast Media

By implementing inclusion and exclusion criteria, 32 articles were included. Today nine types of Gd containing contrast agents are approved for use in Europe and America (8 types in Europe and 6 types in the United States). These preparations include mainly non-specific and extracellular factors; two contrast agents including Gadoxetate (3) and Gadobenate (4, 5) are liver-specific and one is for magnetic resonance (MR) angiography (Gadofosvest). After injection of liver-specific agents and first whole body circulation, they are finally entrapped in the liver due to high affinity toward the hepatocytes. They also partly excrete from bile route (1). A newer relative of Gadofosvest connects to albumin reversibly within

the vessels, so signals created by these contrast agents are better than other nonspecific agents, because of long retention in the vessels area (1,6,7).

Chelating agent of the formulation leads to release of lower amount of Gd in the body thus lowering connection with proteins inside the body and disposal of these factors occur with higher speed in comparison with free Gd ions. As a result, the half-life of these factors in subjects with normally working kidneys is about 1.5 -2 hour (1, 2).

Gadolinium containing contrast media are divided into two categories based on the structure of their chelating parts, linear agents and macrocyclic agents. Each of these categories may include ionic and nonionic structures; yielding four distinct preparations: ionic and linear agents, non-ionic and linear agents, ionic and macrocyclic agents and non-ionic and macrocyclic agents (1) (Table 1).

The Importance of chemical structure

All characteristics of contrast media factors, including efficiency, kinetic properties, stability, side effects and the rate of resolution are directly related to the structure of chelating part of that formulation. By studying structure of a newly introduced contrast agent, as a result, it is possible to predict these specifications (1, 2, 4) (Table 1).

Ionic linear agents have five carboxyl groups in their molecular structure, whereas non-ionic agents have three of them. Increased number of carboxyl group in a structure causes more stability and thus releasing Gd ion inside the body is diminished. Therefore, it may be concluded that linear ionic formulas are more stable than linear and nonionic counterparts (2).

Macrocyclic agents contain polyaminocarboxylate rings in their structure and their flexibility is less than that of linear agents. However, macrocyclic agents are more stable than linear agents (2, 8-10). *In vitro* studies indicate greater stability of ionic macrocyclic contrast agents (with four carboxyl groups) compared with non-ionic macrocyclic factors (with three carboxyl groups). This difference, however, was not confirmed *in vivo* (2, 11).

Stability in the body can be expressed as follows:

Macrocyclic agents > ionic linear agents > non-ionic linear agents

Excess chelating agent in the formula

To avoid potential complications relating to released gadolinium in the body and to band and to enhance Gd disposal, the amount of free excess ligand is added in the instable formulas. Several studies have shown different degrees of complications caused by the same structural formulas with different amount of excess chelating agents (1, 11). So that low stability of GA-CA is related to a large amount of excess chelate that is present in these contrast agents. Presence of excess chelate in gadodismide (non-ionic linear chelate) reduced acute toxicity of formulations

Table 1. Approval status and physicochemical characteristics of gadolinium-based (Gd) MRI contrast agents.

Contrast Agent	Trade Name	Body region(s) approved	Approval	Approved doses (mmol/kg) for body imaging	Approved doses (mmol/kg) for CNS a angiography imaging	Approved doses (mmol/kg) for MR	Approved doses (mmol/kg) for children	Molecular structure/ Charge	Thermodynamic stability constant (log K _{eq})	Osmolality (Osm/kg)	Viscosity (mPa s at 37°C)	TI relaxivity (l/mmol/s), plasma	Half life	Excess ligand (mmol/l)	Classification
Gadopentetate dimeglumine;	Magnevist®	CNS, whole body	USA, EU, Japan	0.1	0.1-0.2	0.1-0.3	0.1	Linear/Ionic	22.1	1.96	2.9	4.9	10 min	1	Least stable
Gadodiamide	Omniscan®	CNS, whole body	USA, EU, Japan	0.1-0.3	0.1-0.3	0.1-0.3	From 6 months: 0.1	Linear/Non Ionic	16.9	0.65	1.4	4.8	35 s	25	Least stable
Gadoterate meglumine	Dotarem®	CNS, whole body	EU	0.1	0.1-0.3	0.2	0.1	Cyclic/Ionic	25.8	1.35	2	4.3	9 h, 60 h, >1 month	0	Most stable
Gadoteridol	ProHance®	CNS, whole body	USA, EU, Jpn	0.1-0.3	0.1-0.3	Not approved	More than 2 years: 0.1; 6 months-2 years: caution; Less than 6 months: contraindicated	Cyclic/Non-ionic	23.8	0.63	1.3	4.6	3 h	0.5	Most stable
Gadobutrol	Gadovist®	CNS	EU	Not approved	0.1-0.3	Not approved	Not approved	Cyclic/Non-ionic	21.8	1.6	4.96	5.6	90 min 18 h	1	Most stable
Gadobenate dimeglumine	MultiHance®	CNS, liver	USA, EU	Liver: 0.05	0.1	Not approved	Not approved for less than 18 years	Linear/Ionic	22.6	1.97	5	9.7	1.17-2.02 h	0	High relaxivity agent
Gadoversetamide	OptiMARK®	CNS, liver	USA	0.1	0.1	Not approved	Not approved for less than 18 years	Linear/Non-ionic	16.6	1.11	2	3.9	80-120 min	50	Least stable
Gadoxetic acid	Primovist®(Europe), Eovist®(USA)	Liver	USA, EU	0.025 or 0.1 ml/kg	Not approved	Not approved	Not approved for less than 18 years	Linear/Ionic	23.46	0.688	1.19	8.4	-	-	-
Gadofosveset	Vasovist®	Abdominal and limb vessels	EU	Not approved	Not approved	MRA 0.03	Not approved for less than 18 years	Linear/Ionic	N/A	0.70-0.95	2.7-3.3	33.4-45.7	29 min	-	high relaxivity agent

CNS; Central Nervous System, USA: United State of America, EU: Europe, Jpn: Japan, MRI: Magnetic Resonance Imaging.

that have no excess chelate (8, 12,13). There is no need for excess ligand in macrocyclic agents (1).

In addition to the above mentioned factors affecting the stability of formulations, certain of special conditions within the body may occur that can lead to more instability, including Trans metallation and concentration of free phosphate in the body (1).

1 - Trans-metallation

When trans-metallation phenomenon takes place, further instability of contrast media may be expected *in vivo*. In this phenomenon, the Gd used in these formulas may be substituted by cations such as Zn, Ca, Cu and Fe due to their higher levels in the body. Zn, in particular, has been suggested to be the most important agent in trans-metallation (1, 14).

Gadolinium released from formulations bands with endogenous anion and deposits in different tissues, leading to increased half-life of Gd (15).

2 – Concentration of free phosphate in the body

In several studies, it has been shown that high levels of phosphate in the body increase the releasing rate of Gd from nonionic-linear formula by 100 times, ionic linear formula by 12-30 times. This phenomenon, however, cannot affect the amount of Gd release from the macrocyclic formulations (16, 17). This phenomenon is of particular importance in patients with compromised kidneys, as well as in patients are on hemodialysis. Use of Gd in such cases require special caution.

Dosing of contrast agents

An overall dose recommendation for administration of contrast media is 0.1 mmol / kg of body weight. In some special instances (e.g. angiography) higher doses may be required (0.2-0.3 mmol /kg) (1). Injection speed is set to 2-3 ml / s (1).

Excretion of gadolinium-based contrast agents (Gd-CA)

In people with normal renal function, 98% of injected contrast agent excretes from the body within 24 hours. Bile excretion happens with three preparations, as well, including Magnevist (2-4% bile excretion), Primovist (50% bile excretion), and Vasovist (9% bile excretion) (1). This bile excretion is important particularly in patients with compromised renal function (7, 18–21).

Side effects

Side effects of Gd-CA can be divided as acute and chronic based on the time of development (9).

Acute complications

Acute complications include feeling cold, numbness, itching at the injection site, nausea and vomiting and headache and dizziness (22). By adhering to the recommended dose of 0.1-0.2 mmol/kg, their prevalence is about 0.07-2.4% (17, 23). In rare cases anaphylaxis

reaction has been also reported (incidence: 0.01-0.001%) (17, 23).

When a History of previous sensitivity to Gd-CA exists, the likelihood of repeated reaction raises by eight times.

History of asthma and hypersensitivity to food and drugs also increases the risk of unwanted reactions by almost 3.7%. There is not a proven cross-sensitivity between Gd and iodinated contrast agents (23).

Extravasation

The prevalence of extravasation is about 0.05 percent of cases. Because of a rather low volume of agent used, the incidence is less than that by iodinated contrast agents (1).

Non-ionic agents have less osmolality and less necrosis happens compared with ionic agents (1).

Chronic or late complications

-Nephrogenic Systemic Fibrosis (NSF)

NSF is one of the remarkable side effects attributed to Gd-CA (24-27). The prevalence of this complication with various agents differs significantly. The prevalence of this complication is less with more stable agents and low free Gd release (10).

In various studies, the prevalence of NSF after contact to Gadodiamid in patients with decreased renal function is about 3-7%. After the first contact in stage V chronic kidney disease (CKD) patient this complication rate is 12%, with an increase to 36% after second injection (10).

According to Center for Disease Control and Prevention report (28), the prevalence of NSF in patients under hemodialysis is more than peritoneal dialysis (10). NSF may develop from the first day of injection up to the next 2-3 months, but it is generally classified as a late complication.

NSF symptoms initially include pain, itching, inflammation and erythema more often in the legs, and then subcutaneous tissues become impassive with woody face and brown color. Fibrosis cans occur in internal organs (diaphragm, muscles, liver, and kidney). Severe NSF can lead to dramatic weakness and even death in some cases (10).

• *People at risk to create NSF*

High risk cases for NFS are patients with chronic renal failure (stage IV and V with glomerular filtration rate, GFR <30), patients with acute renal failure, patients on dialysis and patients with decreased renal function with severe liver problems (candidates for liver transplantation) (10).

Patients with chronic renal failure (stage III) and children under 1 year are considered low risk patients for NSF (10).

• *Recommend strategies to reduce the incidence of NSF*

For all candidates of MR imaging with Gd based contrast agents, Serum creatinine and glomerular filtration

rate (GFR) must be calculated before the administration of the agent. In CKD stages IV-V, a minimum dose of stable factors should be used at the discretion of the attending physician(s) for using contrast agent (10, 23). For patients at risk of NSF, dialysis can accelerate the excretion of contrast media from the body. Almost nine hours of dialysis (3 sessions) is necessary for near complete removal of the contrast agent (10, 22). For patients on the dialysis who have been recommended that their dialysis session should be conducted after the injection of these agents, there is no indication to start dialysis just for removing of Gd-CA. By increasing use of macrocyclic agents in recent years, the prevalence of NSF has dropped significantly (10, 22).

Efficacy of Gd-CA

Due to having seven unpaired electrons in its structure, Gadolinium has strong magnetic properties and can shorten longitudinal (T_1) and transverse (T_2) relaxivity times after exposure to magnetic fields, resulting clearer image than without the application of imaging contrast agents. The chemical structure of these factors plays an important role in establishing the number of places available for the communication between water molecules and Gd, which has an important role in the magnetic performance of these agents (29). Whatever T_1 and T_2 times decreased and relaxivity ($1/T$) increased by contrast media, they can produce better resolution and brighter image (1). The overall efficacy of these agents is related to two factors, relaxivity and concentration. Increasing doses of these agents can also create a better resolution particularly for application in specific situations (such as in small vessel angiography). Studies have shown that agents with higher concentration can be useful by lower injection volume and can create better images (17, 29). In reviews and studies, no significant difference in diagnostic performance between these factors has been reported; three factors Gadovist, MultiHance, Primovist have somewhat higher relaxivity. This property of MultiHance is because of more albumin binding and longer survival is longer in vessels (17).

Application of Gd-CA in pregnancy and lactation

Teratogenic effects of these agents have been shown in animal studies; but this effect hasn't been seen in a study with small sample size in pregnant women. Due to insufficient information and studies in this area, using these agent in the first three months of pregnancy isn't permitted (30) and if imaging is necessary after this time, more stable agents should be used (1, 29, 30).

By application of this Gd-CA during breast feeding less than 0.04 percent of intravenous doses is excreted into milk during 24 hours, which is much lower than toxic concentrations for infants, so mothers can continue breast feeding. If the mother doesn't want to do, it is

recommended that breast milk is discarded for 24 hours after injection of contrast media and the stable agents

(macrocyclic) should be injected for a lactating mother (32).

Conclusion

The differences between the physicochemical properties, kinetic and thermodynamic stability, side effects of Gd-CA have an impact on their applications in clinical diagnosis. In vitro data has shown that the macrocyclic compounds are the most stable Gd-CA and the prevalence of NSF has decreased by increasing the use of macrocyclic agents in recent years. Also in pregnancy and lactating women a stable macrocyclic agent is recommended.

Future perspective

The ideal MRI contrast agent will give the contrast agent that has a neutral tissue- or organ-targeting property with high relaxivity and specificity, low toxicity and side effects, prolonged intravascular duration and excretion time, high contrast enhancement with low dose and minimal cost.

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