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Professor Special Lecture: 76th Annual Meeting of the Medical Society of Toho University

Review Article

Imaging Studies Using Contrast Media: Are Contrast Media a Risk?

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ABSTRACT: Iodinated contrast media (ICM) and gadolinium-based contrast media (GBCM) have been widely used in imaging studies. Although their chemical forms are different, adverse reactions can be similar in some cases and different in others. ICM has both ionic and nonionic forms and can cause acute and late adverse reactions, including anaphylaxis. Patients with a history of hypersensitivity to iodine or ICM and those with serious thyroid disease are contraindicated. Also, patients with a history of active bronchial asthma are found to be at a higher risk of developing adverse reactions. Biguanides used for the treatment of diabetes mellitus should be withheld for 2 days before and 2 days after the administration of ICM. Warming ICM before injection is known to decrease the risk of adverse reactions. Premedication protocols using steroids may reduce the risk of developing acute adverse reactions in some patients. Contrast-associated acute kidney injury (CA-AKI) is a potential risk for patients with severe renal insufficiency, dehydration, advanced age, and diabetes mellitus. Preventive measures for CA-AKI include reducing the amount of contrast medium administered and intravenously administering normal saline before and after the contrast scan. Meanwhile, GBCM has adverse reactions similar to ICM such as anaphylaxis and some different adverse reactions like nephrogenic systemic fibrosis (NSF). Serious thyroid disease and biguanides are not risks of adverse reactions for GBCM. NSF is known to be a debilitating condition that is associated with the use of GBCM in patients with reduced renal function. Therefore, GBCM should be avoided in patients with reduced renal function. Deposition of gadolinium after GBCM administration even in patients with normal renal function has been reported, and indication for administration of GBCM should be carefully evaluated. Imaging studies using contrast media may involve potential risks, but healthcare professionals can prevent and minimize these risks by considering patient medical histories, taking preventive measures, and administering the appropriate contrast media.

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KEYWORDS: contrast media, ICM, GBCM, adverse reaction

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Introduction

There are two contrast media widely used in imaging studies: iodinated contrast media (ICM) used in computed tomography (CT) and angiography and gadolinium-based contrast media (GBCM) used in magnetic resonance imaging (MRI). ICM and GBCM have completely different compositions. However, their adverse reactions and responses to their adverse reactions may be similar in some ways and different in others. This article describes the types of iodine contrast media and gadolinium contrast media, their adverse reactions, prevention of adverse reactions, and safe use of contrast media.

1. ICM

ICMs come in ionic and nonionic forms and monomeric and dimeric forms. Ionic contrast media are dissolved in water to form two ions, resulting in high osmolarity. There have been reports of deaths due to accidental intrathecal administration of ionic contrast media.[1] Therefore, caution is required when using ionic contrast media. Currently, ICMs widely used in CT and angiography are nonionic, monomeric contrast media.

1) Adverse reactions

Adverse reactions that may occur during or after contrast media injection include adverse reactions of the contrast medium itself, adverse reactions associated with the contrast injection technique, and symptoms resulting from the patient's condition. The ICM's adverse reactions may include renal and non-renal reactions including anaphylaxis. Anaphylaxis is known as an immune-mediated hypersensitivity reaction, but contrast-induced anaphylaxis is known to occur even after the first dose. For this reason, it was referred to as an anaphylaxis-like symptom, but because it is difficult to distinguish between the two, both are now referred to as anaphylaxis.

There are two types of non-renal adverse reactions: acute adverse reactions that develop within 1 hour after contrast administration and late adverse reactions that develop within 1 hour to 1 week after contrast administration.[2] Acute adverse reactions occur in 3.13% of nonionic cases, of which severe reactions are noted in 0.04%.[3]

2) How to prevent non-renal adverse reactions

The package insert for ICM lists patients with a history of hypersensitivity to iodine or ICM and patients with serious thyroid disease as contraindications. In addition, patients with bronchial asthma are listed in the precautions for patients with certain backgrounds. In the list of drug interactions, the concomitant use of biguanide diabetes medications is listed as a precaution. Therefore, patient history of these conditions should be confirmed before administration of ICM.

For patients with a history of hypersensitivity to iodine or ICM, alternative tests without ICM administration should be selected, or pretreatment should be performed if previous adverse reactions are mild to moderate, or a different contrast medium should be selected.

ICM is contraindicated in patients with severe thyroid disease because the self-regulatory mechanisms for iodine overload may not function, which may only worsen the symptoms.

For patients with bronchial asthma, it is necessary to consider whether the disease is active or controlled by medication or other means. The patient can be considered clinically cured if the patient has been asymptomatic or untreated for at least 5 years; in such case, ICM can be considered to be used safely. If the patient's symptoms are under control and the contrast medium is judged to be of high benefit, then iodine contrast media should be used after premedications.

If the patient is taking biguanides for diabetes medication, it should be withheld from 2 days before to 2 days after contrast administration due to the risk of lactic acidosis.

In addition, the incidence of adverse reactions is said to be higher at younger ages and with first-time administration.[4] For this reason, contrast media should be administered with caution, especially when administered at younger ages and for the first time. It has been reported that the incidence of adverse reactions is higher when the contrast medium is kept at room temperature than when it is warmed up to 37℃.[5] Therefore, it is necessary to heat the contrast media to 37℃ before use to lessen any adverse reaction.

3) Premedications

Pretreatment includes steroid premedication in order to reduce the risk of developing acute adverse reactions to ICM. Premedication protocols include prednisone 50 mg given orally 13, 7, and 1 hour before contrast administration or methylprednisolone 32 mg given orally 12 and 2 hours before contrast administration.[6]

4) Renal adverse reactions: contrast-associated acute kidney injury (CA-AKI)

CA-AKI, previously known as contrast-induced nephropathy, is defined as "an increase in serum creatinine of more than 0.3 mg/dL (or 26.5 μmol/L) or 1.5 times baseline with no other cause of renal function deterioration within 48-72 hours after intravascular administration of contrast media," as per the European Society of Urogenital Radiology (ESUR) guidelines.[7] For domestic guidelines, the Japanese Society of Nephrology, the Japan Radiological Society, and the Japanese Society of Cardiology have jointly applied modifications to a guideline concerning the use of ICM in patients with renal impairment in 2018,[8] and this guideline is currently used in clinical practice.

The main risk factors for CA-AKI are severe renal insufficiency, dehydration, advanced age, and diabetes mellitus.

5) Prevention of CA-AKI

For patients with severe renal insufficiency, preventive measures are recommended when renal function is below estimated glomerular filtration rate (eGFR) ＜30 mL/min/1.73 m^2. This includes reducing the amount of contrast medium administered and intravenously administering normal saline before and after the contrast scan. It is recommended that normal saline be infused at 1 mL/kg/h for 6 hours before contrast and 1 mL/kg/h for 6 to 12 hours after ICM administration.

6) Renalism

This is described as an overreaction to CA-AKI, in which tests and treatments that should have been performed are withheld because of concerns with regard to CA-AKI. Patients whose testing and treatment are withheld because of this overreaction may have a poorer prognosis than patients who undergo timely testing and treatment. Therefore, it is necessary to weigh the benefits of the tests/treatment against the disadvantages, such as CA-AKI, before deciding which tests/treatment should be performed.

2. GBCM

The contrast agent widely used in MRI is GBCM. This contrast agent is a chelated form of the metal gadolinium and is normally excreted in the urine. GBCM can be divided into two types based on molecular structure: linear and macrocyclic. However, gadolinium contrast agents with a macrocyclic structure are now mainly used to reduce the risk of nephrogenic systemic fibrosis and deposition.[9]

1) Adverse reactions to GBCM

The mechanism of adverse reactions to GBCM is similar to that of ICM, but the frequency is one-third that of ICM.[10] The package insert of GBCM lists patients with a history of hypersensitivity to the components of GBCM as contraindications. In addition, patients with bronchial asthma are listed in the precautions for patients with specific backgrounds. Unlike the package inserts for ICM, the package insert for GBCM does not list patients with serious thyroid disease as a contraindication, nor does it list biguanide as a drug that has risks of interactions. In addition, there is mention of renal adverse reactions.

2) How to prevent non-renal adverse reactions

The main preventive measure for the non-renal side effects of gadolinium contrast media is to check the patient for a history of hypersensitivity to GBCM and for a history of bronchial asthma. The response to a history of these adverse reactions is the same as for adverse reactions to ICM, and premedication protocols are also deemed the same.

3) Renal adverse reactions

Renal function must be confirmed before the administration of GBCM, and this contrast medium should not be administered to patients with renal failure.

4) Nephrogenic systemic fibrosis

This disease is associated with the use of gadolinium contrast media in patients with reduced renal function. Symptoms of this disease include skin swelling, stiffness, and pain that develop several days to several months after GBCM administration, and as the disease progresses, joint contractures in the extremities may occur, severely limiting activity.[11] Currently, there is no established treatment for this disease, and deaths have been reported. However, reports of this disease have drastically reduced due to strict restrictions on the use of GBCM in patients with reduced renal function.

5) Deposition of gadolinium after GBCM administration

Deposition of gadolinium in the body after administration of GBCM has been noted in recent years. This was first reported as deposition of gadolinium in the globus pallidus and cerebellar dentate nucleus, mainly after repeated administration of linear GBCM.[12] Subsequently, deposition in all parts of the body has been reported,[13] but there have been few reports of adverse health effects. It has been reported that gadolinium depositions occur even in patients with normal renal function[14];

therefore, the administration of GBCM must be carefully evaluated.

Conclusion

There is no reliable and safe way to predict serious adverse reactions to contrast media. Therefore, prevention and pretreatment are important, and the significance of checking patient background before administration needs to be reaffirmed. ICM requires caution in young patients and patients who undergo contrast media injection for the first time. GBCM requires confirmation of the type of contrast media. Thus, it should be emphasized that contrast agents must be administered under appropriate circumstances.

Conflicts of interest: Tatsuya Gomi is an advisor at FUJIFILM Healthcare Corporation

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