Standards for intravascular contrast agent administration to adult patients

Second edition
The Royal College of Radiologists (RCR), a registered charity, exists to advance the science and practice of radiology and oncology.

It undertakes to produce standards documents to provide guidance to radiologists and others involved in the delivery of radiological services with the aim of defining good practice, advancing the practice of radiology and improving the service for the benefit of patients.

The standards documents cover a wide range of topics. All have undergone an extensive consultation process to ensure a broad consensus, underpinned by published evidence where applicable. Each is subject to review four years after publication or earlier if appropriate.

The standards are not regulations governing practice but attempt to define the aspects of radiological services and care which promote the provision of a high-quality service to patients.

Current standards documents

Standards for radiofrequency ablation (RFA)
Standards for the introduction of new procedures and new devices
Standards for providing a 24-hour diagnostic radiology service
Standards for patient confidentiality and PACS
Standards for providing a 24-hour interventional radiology service
Standards for the communication of critical, urgent and unexpected significant radiological findings
Standards for Self-assessment of Performance
Standards for Radiology Discrepancy Meetings
Standards in Vascular Radiology
Standards for Ultrasound Equipment
Standards for Patient Consent Particular to Radiology
Standards for the Reporting and Interpretation of Imaging Investigations
Cancer Multidisciplinary Team Meetings – Standards for Clinical Radiologists
360° Appraisal – Good Practice for Radiologists
Individual Responsibilities – A Guide to Medical Practice for Radiologists
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Foreword

These revised guidelines are necessary because of ever-changing literature about both iodinated and gadolinium contrast agents. The Royal College of Radiologists (RCR) would like to thank the original authors, Professors Sameh Morcos and Peter Dawson along with Drs Mark Downes and Paul Spencer who were largely responsible for the revision. The RCR would also like to thank the members of the Professional Support and Standards Board who also made significant contributions.

This document replaces previous advice given in Standards For Iodinated Intravascular Contrast Agent Administration To Adult Patients BFCR(05)7, which is now withdrawn.

Dr Tony Nicholson

Dean of the Faculty of Clinical Radiology
The Royal College of Radiologists
Introduction

The use of intravascular contrast agents has increased dramatically in recent years. The potential risks of intravascular administration of contrast agents must be weighed against the potential benefits. Withholding agents may deprive patients of the benefits of valuable diagnostic information or necessary therapy. These guidelines aim to provide guidance on how contrast agents may be used as safely as possible.

This document deals with administration of contrast agents to adult patients. For children and neonates, a paediatric radiologist should be consulted.

General safety issues

- Non-ionic, low or iso-osmolar agents are five to ten times safer than the older, high osmolar ionic agents.¹
- Both low osmolar iodinated and gadolinium contrast agents are associated with a very low rate of adverse effects (0.15% for low osmolar contrast and 0.04% for gadolinium contrast).²
- Most adverse effects are mild and can be managed in the radiology department.²
- A major life-threatening contrast reaction is rare. The incidence of severe reactions with non-ionic agents is 0.04% and very serious reactions is 0.004%.¹²
- To minimise risk, it is important to identify individuals for who there is an increased risk of an adverse event.
- Appropriate steps to reduce the risk of contrast reactions should always be taken.
Practical safety issues

- An appropriately trained doctor should be immediately available to deal with any severe reaction. This may require calling the ‘crash team’ within the healthcare organisation.
- An individual trained in recognising and treating severe contrast reactions, including anaphylaxis, should be immediately available in the department. This could be a registered nurse or radiographer or other appropriately trained healthcare professional.
- In the presence of risk factors, the decision about contrast agent administration should be taken only by the radiologist supervising the procedure.
- In view of the risk of contrast nephrotoxicity, dehydration of patients prior to contrast agent administration is undesirable and should be avoided.
- Facilities for the treatment of acute adverse reactions should be readily available and regularly checked.
- A patient should not be left alone or unsupervised in the first five minutes after an injection of the contrast agent.
- It is advisable that the patient remains on the premises for at least 15 minutes after the injection. Most severe reactions occur during this time. In patients with an increased risk of a reaction, this should be doubled to 30 minutes.
- All contrast reactions, with details of their nature, severity and the agent used, should be included in the radiological report and updated in the patient’s hospital notes and on the radiology information system (RIS).

Prescribing contrast

A formal record of the decision to inject intravenous contrast agents should be made before administration. How this is achieved will depend on local circumstances, but may include:

- Setting up a Patient Group Directive to cover specific scan protocols
- A formal written record by the radiologist, signed and dated on the request and either filed in the radiology department or scanned into the RIS
- Recorded electronically directly into RIS as part of the vetting process
- A formal prescription on the patient’s drug chart.
Patient information and consent

The patient should always be fully informed about any procedure and understand what it will involve. Appropriate patient information leaflets should be available in the department. The individual administering the contrast agent must check that there are no contraindications to its administration and ensure that the patient understands that it is to be given and agrees to proceed.

Identifying patients at increased risk for contrast reaction

The ultimate responsibility for contrast agent administration rests with the person who prescribes it, although delivery of the injection is frequently delegated to others under local rules and protocols.

Essential information which should be sought from the patient before a contrast injection includes history of:

- Previous contrast reaction
- Asthma
- Renal problems
- Diabetes mellitus
- Metformin therapy.

Ideally, this information will be available when the examination is requested but should always be checked in the department before injection.

To minimise the risk of contrast nephrotoxicity, the estimated glomerular filtration rate (eGFR) or, as a minimum, the serum creatinine level should be available in all non-emergency patients. In patients who have a stable clinical condition, an eGFR within the previous three months is satisfactory. Patients who have an acute illness or who are known to have renal disease should have an eGFR or serum creatinine obtained from the previous seven days.

Particular care should also be taken in patients who are acutely or severely unwell, such as with hypotension or hypovolaemia. These cases are likely to be carried out on an urgent or emergency basis and the potential risks of contrast agent use must be weighed against the potential benefits.
Recommendations for contrast use in patients at increased risk of contrast reaction

History of previous contrast reaction

Caution should be exercised when there is a previously reported moderately severe (such as bronchospasm or urticaria requiring treatment) or a severe reaction (for example, laryngeal or angio-neurotic oedema, severe bronchospasm or collapse).3,4

Advice

Determine:
- The exact nature of the previous reaction
- The agent used on that occasion.

Re-examine the need for the use of the contrast agent, with respect to an unenhanced study or other potential methods of investigation.

Assess the risk–benefit ratio of the procedure, bearing in mind that a non-diagnostic examination may be as detrimental to the patient as the perceived risk from contrast exposure.

If the injection is deemed necessary:
- Use a different, non-ionic low or iso-osmolar agent to that previously used
- Maintain close medical supervision
- Leave the cannula in place and keep the patient under observation for 30 minutes after the procedure
- Be ready to treat any adverse reaction promptly and ensure that emergency drugs and equipment are available.

Asthma

Asthmatics are at an increased risk of severe contrast reactions by a factor of six with low or iso-osmolar non-ionic contrast agent and by a factor of ten with high osmolar agents.1

Advice

Determine:
- Whether the patient has true asthma or chronic obstructive pulmonary disease (COPD)
- Whether the asthma is currently well controlled.

If the patient is wheezy, or reports that their asthma is currently not well controlled and the examination is not urgent, it should be deferred and the patient referred back for appropriate medical therapy.

If the asthma is well controlled, reassess the need for intravascular contrast with respect to an unenhanced study or other potential methods of investigation.

If the injection is deemed necessary:
- Use a non-ionic low or iso-osmolar agent
- Maintain close medical supervision
- Leave the cannula in place and observe the patient for 30 minutes after the procedure
- Be ready to treat any adverse reaction promptly and ensure that emergency drugs and equipment are available.
Multiple allergies or a documented severe allergy requiring therapy

Individuals with multiple, well-documented allergies, or a single very severe allergy are at increased risk.¹ ³ ⁴

Advice

Determine the nature of the allergies and their sensitivity. (NB: there is no specific cross reactivity with shellfish or topical iodine in acute reactions.)

In those with multiple or severe allergy, re-examine the need for contrast administration with respect to an unenhanced study or other potential methods of investigation.

The potential risks of intravascular administration of contrast medium must be weighed against the potential benefits.

If the injection is deemed necessary:

- Use a non-ionic low or iso-osmolar agent
- Maintain close medical supervision
- Leave the cannula in place and observe the patient for 30 minute after the procedures
- Be ready to treat any adverse reaction promptly and ensure that emergency drugs and equipment are available.

There is no conclusive evidence of benefit for the prophylactic use of steroids in the prevention of severe reactions to contrast agents.³ ⁴

Renal disease, diabetes mellitus and conditions associated with renal impairment

In the presence of renal impairment, all contrast agents – including non-ionic low osmolar, iso-osmolar agents and high-volume gadolinium-based contrast agents – are nephrotoxic.

The risk of contrast nephrotoxicity is related to the extent of pre-existing renal impairment, the dose of contrast agent administered and the state of hydration of the patient. The combination of renal impairment and diabetes mellitus carries significant risk.

Congestive heart failure, old age (>70 years) and concurrent administration of nephrotoxic drugs are also risk factors for contrast nephrotoxicity.⁵–⁷

eGFR measurement should be used to identify patients at risk of contrast nephrotoxicity. It should be noted that serum creatinine is an imperfect indicator of renal function and the majority of laboratories now supply an eGFR.

A recent eGFR level should be available for all patients attending for an elective examination requiring contrast with a history of renal disease or diabetes (or a serum creatinine estimation as a minimum requirement).

eGFR measurement is required in all patients undergoing angiographic procedures⁵–⁶ in which, on average, higher doses of contrast agent are used and in which the kidney may be exposed to higher concentrations via the intra-arterial route.

A guide level of an eGFR below 60 ml/min/1.73 m² has been used in the literature to indicate renal impairment, but the level chosen to trigger special precautions may be set locally after discussion involving the local radiologists and nephrologists.

Advice

The need for investigation/intervention should be re-examined in the light of an unenhanced study or alternative investigation/therapy, and the severity of the degree of renal impairment.

The risk–benefit of the procedure should be assessed.

If the administration of contrast medium is deemed necessary, steps should be taken to reduce the risk.
Risk reduction steps include:

- Using the smallest possible dose of low osmolar non-ionic monomeric or iso-osmolar non-ionic dimeric contrast medium
- Ensuring the patient is well hydrated before and after the procedure either orally or, in the case of high dose or intra-arterial administration, intravenously.\textsuperscript{5,6}

Iso-osmolar non-ionic dimeric contrast agents are currently available, but the exact preventative role in terms of contrast-induced nephropathy of these agents is not yet clear.\textsuperscript{9,10} There is general acceptance that iso-osmolar agents produce less patient discomfort than low osmolar agents particularly in intra-arterial studies.

There is insufficient evidence at this stage to advocate any pharmacological treatment attempting to reduce the incidence of contrast-induced nephropathy.

**Metformin**

Metformin is not recommended for use in diabetics with renal impairment because it is exclusively excreted via the kidneys. Accumulation of metformin may result in the development of the serious complication of lactic acidosis. There is a lack of any valid evidence that lactic acidosis is really an issue after iodinated contrast in patients taking metformin. The problems caused to patients and clinicians by stopping the drug and its increasing use in poorly controlled diabetic patients regardless of renal function, have been considered in formulating this advice. It does, however, remain the case that renal function should be known in patients taking metformin who require intravenous or intra-arterial contrast agents.

**Advice**

There is no need to stop metformin after contrast in patients with serum creatinine within the normal reference range and/or eGFR >60 ml/min. If serum creatinine is above the normal reference range or eGFR is below 60, any decision to stop it for 48 hours should be made in consultation with the referring clinic.
Other special cases

Pregnancy

In exceptional circumstances, iodinated contrast may be administered during pregnancy. Due to the small theoretical risk of thyroid suppression in the fetus, thyroid function should be measured in the first week after birth.11

Lactation

A very small percentage of the injected dose enters the breast milk and virtually none is absorbed across the normal gut, and no special precaution or cessation of breastfeeding is required.11

Thyroid

Intravascular contrast should not be administered if the patient is hyperthyroid. In patients with thyroid cancer, the use of iodinated contrast agents will preclude therapeutic radio-iodine treatment for two months.12 MRI is the preferred staging method in these patients. Isotope thyroid imaging should also be avoided for two months after intravascular administration of iodinated contrast injection.13

Interleukin-2 treatment

A specific risk of delayed skin rash is associated with interleukin-2 therapy. Oncologists should be informed that they should always indicate if the patient is on this drug when referring them for a contrast injection.14

Gadolinium contrast agents

Gadolinium-containing contrast agents are associated with a varying degree of risk of nephrogenic systemic fibrosis. See advice below to minimise risk in the following vulnerable groups:

- Patients with renal impairment
- Patients in the perioperative liver transplantation period
- Infants, neonates and the elderly
- Women who are pregnant or breastfeeding.

High-risk gadolinium-containing contrast agents are contraindicated in patients with severe renal impairment, patients in the perioperative liver transplantation period and in neonates.

Nephrogenic systemic fibrosis (NSF) is a serious and life-threatening condition characterised by the formation of connective tissue in the skin which becomes thickened, coarse and hard, sometimes leading to contractures and joint immobility. Patients with NSF can have systemic involvement of other organs, including the lungs, liver, muscles and heart. The Royal College of Radiologists published guidance on gadolinium-based contrast agents and NSF in 2007.15

Some gadolinium contrast agents are more associated with NSF than others. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has classified these as low, medium and high risk.16
Advice

The following risk minimisation measures should be used for gadolinium-containing contrast agents. This advice is adapted from the current Medicines and Healthcare products Regulatory Agency (MHRA) advice.17

Renal function monitoring

Renal function should be tested in all patients receiving high-risk agents, and is generally advisable for patients receiving medium-risk agents. It is particularly important to screen patients aged 65 years or older or patients with chronic diseases such as diabetes which are associated with renal failure.

Renal impairment

For patients with severe renal impairment (eGFR <30 ml/min/1.73 m²), use of a high-risk agent is contraindicated. If, after clinical review, use of a low-risk agent cannot be avoided or if it is necessary to use a medium-risk agent, a single lowest dose possible can be used and should not be repeated for at least seven days.

For patients with moderate renal impairment (eGFR 30–59 ml/min/1.73 m²), if, after clinical review, it is necessary to use a high-risk agent, a single lowest dose possible can be used and should not be repeated for at least seven days.

Perioperative liver transplantation period

Use of a high-risk agent is contraindicated. If the use of a low-risk agent cannot be avoided or if it is necessary to use a medium-risk agent, a single lowest dose possible can be used and should not be repeated for at least seven days.

Breastfeeding

Discontinue for at least 24 hours after use of a high-risk agent. The decision of whether to continue or suspend breastfeeding for 24 hours after use of a medium-risk or low-risk agent should be at your discretion in consultation with the mother.

Pregnancy

Use of any gadolinium-containing contrast agent is not recommended unless absolutely necessary.

Haemodialysis

There is no evidence to support the initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

Recording of the agent used

When they become available, peel-off tracking labels found on the vials, syringes or bottles should be stuck onto the patient record to accurately record the name of the gadolinium contrast agent used. The dose used should also be recorded.

Suspected adverse reactions should be reported on a Yellow Card to the MHRA.18
The treatment of reactions

Simple guidelines for the treatment of reactions are presented below.19,20

Nausea/vomiting

- **Transient**: supportive treatment.
- **Severe, protracted**: appropriate anti-emetic drugs should be considered.

Urticaria

- **Scattered, transient**: supportive treatment, including observation.
- **Scattered, protracted**: appropriate H1-antihistamine intramuscularly, orally or intravenously should be considered. Drowsiness and/or hypotension may occur.
- **Profound**: consider adrenaline 1:1000, 0.1–0.3 ml (0.1–0.3 mg) intramuscularly. Repeat, as needed.

Bronchospasm

- Oxygen by mask (6–10 l/min).
- β-2-agonist metered dose inhaler (2–3 deep inhalations).
- Adrenaline:
  - **Normal blood pressure**: adrenaline 1:1000, 0.1–0.3 ml (0.1–0.3 mg) intramuscularly. Use smaller dose in a patient with coronary artery disease or elderly patient
  - **Decreased blood pressure**: adrenaline 1:1000, 0.5 ml (0.5 mg) intramuscularly.

Laryngeal oedema

- Oxygen by mask (6–10 l/min).
- Adrenaline 1:1000, 0.5 ml (0.5 mg) intramuscularly. Repeat, as needed.

Hypotension

- Isolated hypotension:
  - Elevate patient’s legs
  - Oxygen by mask (6–10 l/min)
  - Intravenous fluid: rapidly, normal saline or lactated Ringer’s solution
  - If unresponsive: adrenaline 1:1,000, 0.5 ml (0.5 mg) intramuscularly. Repeat, as needed.
- Vagal reaction (hypotension and bradycardia):
  - Elevate patient’s legs
  - Oxygen by mask (6–10 l/min)
  - Atropine 0.6–1.0 mg intravenously, Repeat, if necessary, after 3–5 minutes, to 3 mg total (0.04 mg/kg)
  - Intravenous fluids: rapidly, normal saline or lactated Ringer’s solution.
Generalised anaphylactoid reaction

- Call for resuscitation team.
- Suction airway, if needed.
- Elevate patient’s legs, if hypotensive.
- Oxygen by mask (6–10 l/min).
- Adrenaline: 1:1000, 0.5 ml (0.5 mg) intramuscularly.
- H1 blocker, for example, diphenhydramine 25–50 mg intravenously.

Contrast medium extravasation

- Record details of the incident with management advice in the report and notes.
- Elevate the affected limb.
- Apply ice packs to the affected area.
- If symptoms do not resolve quickly, admit and monitor.
- Skin blistering, paraesthesia, altered tissue perfusion and increasing or persistent pain >4 hours suggest severe injury. If so, seek surgical advice (plastic surgeon).21–23

Delayed skin reactions

- Skin reactions have been reported up to a week after the administration of contrast medium.14 Symptomatic treatment only is required. The reaction should be recorded in the patient’s record, but it is the case that the status and significance of these reactions are uncertain.
Ultrasound contrast agents (microbubbles)

Background

Microbubble contrast agents all essentially consist of gas bubbles (air, perfluorocarbon and so on) stabilised by a surrounding membrane (phospholipid). These are intravascular agents and are injected intravenously into the antecubital vein and are visualised using one of the contrast agent settings present on any modern ultrasound machine. The advantage of using such a technique, commonly referred to as contrast-enhanced ultrasound (CEUS), is that such an examination can be performed in real time. Its temporal resolution is greater than that of both CT and MRI; it is simple to perform, does not involve radiation and its real-time multi-planar imaging allows prompt diagnosis. In addition, the patient and safety tolerance of these agents is such that these studies can be performed in a repeatable fashion.

It is important to appreciate that as a general rule the same limitations of conventional ultrasound also apply to CEUS; that is, if the baseline scan is poor the CEUS study will be poor and vice versa.

Safety profile

These agents are safe with a low incidence of side-effects.

They are not nephrotoxic and they can be used in all patients independent of renal function or use of metformin.

No specific consideration needs to be given to patients with diabetes mellitus.

The incidence of severe hypersensitivity allergic reaction is less than that of X-ray and MRI contrast agents with the incidence of severe anaphylactic reaction in abdominal applications being quoted as 0.001%.

Contraindications

- Pregnancy
- Breast feeding
- Microbubble agents should not be used within 24 hours of patients receiving extracorporeal shock wave lithotripsy (ESWL) therapy
- Neonates where there is developing sensitive tissue such as eye and brain.

Consideration to use should be given in patients who are critically ill, particularly with severe cardiopulmonary disease and ideally are best avoided in these patients. Such patient groups include recent acute coronary syndrome, clinically unstable ischaemic cardiac disease, acute or class III/IV cardiac failure or severe rhythm disorder, known right to left shunt, severe pulmonary artery hypertension and acute respiratory distress syndrome (ARDS).

Indications

There are a large number of applications for CEUS – please see http://www.efsumb.org/asp/detail00.asp?ref=280&url=/intro/home.asp?ref=1 and http://www.efsumb.org/mediafiles01/ceus-guidelines2008.pdf

Most evidence exists within the liver for the characterisation, detection and monitoring of focal liver lesions. Focal liver lesion characterisation with CEUS has a similar sensitivity and specificity to CT and MRI and is one of its main uses.

Other applications including kidney, bladder, trauma and so on, although less well established, are all currently under evaluation.

Conclusion

In essence, contrast-enhanced ultrasound technique is safe and effective and has numerous applications particularly with regard to the characterisation of focal liver lesions. Its safety profile is much better than agents used in CT and MRI and can help solve many clinical issues particularly in patients where renal function or diabetes may be a consideration.


Approved by the Board of the Faculty of Clinical Radiology: July 2011.


