Diagnostic Imaging Pathways - Contrast Agents: Iodinated Contrast for CT Scans

Iodinated Contrast for CT Scans

In Australia, intravascular contrast media for radiographic procedures are almost exclusively non-ionic (as opposed to ionic) contrast agents. Non-ionic agents are thought to be up to 10 times safer than ionic contrast media. Uses of contrast include intravenous urography, contrast-enhanced CT scans, venography and angiography.

Allergy-Like Reactions

The vast majority of patients tolerate intravascular non-ionic contrast injection well. Severe reactions including shock, cardiac arrest and death from anaphylactic reactions do occur very rarely in about 1 in 100,000 patients. These reactions are not dose-dependent and generally do not involve antibody formation to contrast media. The clinical features of anaphylactic reactions usually manifest within 60 minutes, with the majority developing in the first 5 minutes. Delayed reactions occur up to one week post-injection and generally involve skin rashes without bronchospasm or laryngeal oedema. Symptoms vary between patients and can be classified into system-based categories:

- **Cutaneous**
  - Generalised pruritus, flushing
  - Urticaria (hives) or angioedema
- **Respiratory**
  - Laryngeal oedema (hoarseness, stridor)
  - Bronchospasm (shortness of breath, wheezing)
  - Respiratory failure
- **Cardiovascular**
  - Arrhythmias
  - Conduction disturbances
  - Vasodilatation, increased vascular permeability
  - Hypotension, anaphylactic shock
- **Neurological**
  - Syncope, dizziness
  - Seizures
- **Gastrointestinal**
  - Nausea, vomiting, diarrhoea
  - Abdominal cramps

While the risk of severe reaction is largely unpredictable, factors that predispose to a reaction include: a history of a previous generalized contrast reaction, an atopic history and a history of asthma. 1. Although beta adrenergic blocking medications do not appear to significantly increase the incidence of an anaphylactic contrast media reaction, any such reaction is more likely to be moderate or severe. (This population may also be resistant to adrenaline used in resuscitation and IV glucagon should be used if adrenaline is ineffective). Patients at risk should receive non-ionic contrast agents if iodinated contrast material is needed. 1
Premedication with corticosteroids, with or without antihistamines has been shown to reduce the likelihood and severity of anaphylactic reactions but there is no evidence that it reduces the likelihood of death resulting from a breakthrough anaphylactic reaction. \textsuperscript{1, 2}

Corticosteroids ± antihistamines (eg. prednisolone 50mg orally taken 13 and 1 hour(s) before contrast administration) have been the most widely recommended agents but are not effective if commenced less than 6 hours before the procedure. \textsuperscript{1, 3} Patients should be made aware of the potential risks of contrast media prior to the procedure.

**Contrast Extravasation**

Contrast extravasation is an uncommon and generally benign complication of iodinated contrast injection. It occurs when there is leakage of iodinated contrast material out of the vein and into the surrounding subcutaneous tissues. Because iodinated contrast is cytotoxic (harmful to tissues), it can cause a range of complications. However, extravasation of contrast media into the subcutaneous tissues is uncommon occurring in less than 1% of patients. \textsuperscript{1} Risk factors include use of small veins, fragile or previously damaged veins, obesity and large volume contrast media injections. \textsuperscript{1}

The majority of patients who have contrast extravasation will only exhibit mild symptoms. These manifest as an acute local inflammatory response, including tissue edema, erythema, stinging and tenderness. Some patients may not experience any discomfort. More severe symptoms may also occur such as compartment syndromes, skin ulceration and tissue necrosis. Compartment syndromes occur when there is mechanical compression of the nerves, blood vessels and muscles within a closed compartment within the body. If the compression is not relieved, it can lead to tissue death. It can occur in contrast extravasation after extravasation of large volumes of contrast, or when the extravasation occurs in smaller tissue compartments (such as the back of the wrist). This may require surgery to relieve the pressure.

Contrast extravasation and severe sequelae from them are very rare. Wang et al. found only 475 incidences of contrast extravasation out of nearly 70,000 contrast injections (0.7% incidence). Of the 475, only 12 patients developed moderate or severe injuries as a result of extravasation. Only one patient required surgery to relieve a compartment syndrome involving the dorsum of her hand. The patient had no residual functional impairment on follow-up. Surgical referral is required if serious injury such as cutaneous ulceration, tissue necrosis or compartment syndrome develop. \textsuperscript{1}

Unfortunately, there is no clear consensus as to the most effective treatment for contrast extravasation. Generally, conservative treatments such as limb elevation, cold compresses & application of lanolin are adequate in most cases. \textsuperscript{1} The intravenous cannula should be left in place and the patient instructed to remain under supervision at the facility where contrast media has been administered for at least 15 minutes following contrast media injection. This period should be 30 minutes for patients at increased risk of an anaphylactic reaction. \textsuperscript{1} They should be given clear instructions to re-present to ED if there is any worsening or development of new symptoms. If the patient's symptoms worsen or new neurological/vascular symptoms develop during the observation period, they should be referred to the plastic surgery team for urgent review.

**Contrast Induced Nephropathy (CIN)**

- The risk of contrast-induced acute kidney injury (CI-AKI) remains uncertain for patients with an estimated glomerular filtration rate (GFR) less than 45 mL/min/1.73m\textsuperscript{2}, but if a risk exists, it is
greatest in those with estimated GFR less than 30 mL/min/1.73m².

- There is greatest controversy about the risk of CI-AKI for patients with eGFR less than 30 mL/min/1.73m² with the odds of CI-AKI occurring in this group as a result of a single intravenous dose of iodinated contrast media being either the same as or up to 7 times greater than patients with normal renal function.
- Intra-arterial administration is associated with a higher risk for CI-AKI than is intravenous administration. This may relate both to the usually larger volume of contrast media administered and the potential for renal embolisation.
- No prospective randomised controlled trials have been conducted to test the hypothesis that there is a difference in the likelihood of AKI developing after iodinated contrast media administration in individuals with various levels of pre-existing renal function impairment at the time of contrast administration.

**Risk Factors**

The following guidelines are recommended by the RANZCR:

1. Intravascular iodinated contrast media should be given to any patient regardless of renal function status if the perceived diagnostic benefit to the patient, in the opinion of the radiologist and the referrer, justifies this administration.
2. Emergency imaging procedures requiring contrast media administration e.g. acute stroke, acute bleeding, trauma etc. should not be delayed in order to obtain renal function testing results prior to the procedure.
3. The risk of intravenous contrast media related acute kidney injury (CI-AKI) is likely to be non-existent for patients with eGFR greater than 45 mL/min/1.73m². No special precautions are recommended in this group prior to or following intravenous administration of iodinated contrast media.
4. The risk of intravenous CI-AKI is also very likely to be low or non-existent for patients with eGFR 30 - 45 mL/min/1.73m². Universal use of periprocedural hydration in this group to prevent the theoretical risk of CI-AKI cannot be recommended but patients with impaired function in this range that is acutely deteriorating rather than stable may benefit from this intervention.
5. In patients with severe renal function impairment (eGFR less than 30 ml/min/1.73m²) or actively deteriorating renal function (acute kidney injury) careful weighing of the risk versus the benefit of iodinated contrast media administration needs to be undertaken. Consideration should be given to peri-procedural renal protection using intravenous hydration with 0.9% saline. However, severe renal function impairment should not be regarded as an absolute contraindication to medically indicated iodinated contrast media administration.

**Assessing Renal Function**

Estimation of the actual glomerular filtration rate (GFR) to assess kidney function facilitates the detection, evaluation, and management of kidney disease. Manual estimation of GFR (eGFR) for clinical purposes using creatinine, age, gender and race should use the CKD-EPI creatinine equation (shown below). The Modified Diet in Renal Disease (MDRD) derived eGFR commonly reported in association with serum creatinine in laboratory reports does not take into account patient weight and is unreliable for those who are extremely overweight or underweight. Studies have shown the CKD-EPI creatinine equation to be more accurate than the Modification Diet in Renal Disease (MDRD) Study equation.

The CKD EPI Formula

1. Estimate GFR using the CKD-EPI Formula
2. If GFR is less than 60 mL/min/1.73m², perform additional tests to confirm the diagnosis of kidney disease.
3. If GFR is less than 30 mL/min/1.73m², consider treatment options to prevent further decline in kidney function.

The CKD EPI Formula 1. 5
GFR = $141 \times \min(\text{Scr/?, 1}) \times \max(\text{Scr/?, 1}) \times 1.209 \times 0.993 \times \text{Age} \times 1.018 \times [\text{if female}] \\
\times 1.159 [\text{if black}]$

? = 0.7 if female

? = 0.9 if male

? = -0.329 if female

? = -0.411 if male

\[ \min = \text{The minimum of Scr/? or 1} \]

\[ \max = \text{The maximum of Scr/? or 1} \]

\[ \text{Scr} = \text{serum creatinine (mg/dL)} \]

**Prevention of CIN**

- Identify patients at risk (as above)
- Use alternative modality not requiring contrast administration (if feasible); e.g. non-contrast CT, ultrasound or non-contrast MRI
- Use low-osmolar or iso-osmolar non-ionic contrast
- Use lowest volume feasible
- Avoid repeat injections
- Avoid dehydration
- Discontinue nephrotoxic medications 24-48 hours before contrast administration
- Hydrate the patient: intravenous hydration with normal saline is preferable to oral hydration at a rate of at least 1-2 mL/hr/per kg body weight and should be commenced at least 4 hours prior to the procedure and continued for 4-24 hours post procedure; this may not be appropriate in certain clinical situations (e.g. congestive heart failure) and caution must be applied
- Sodium bicarbonate alone or in combination with intravenous 0.9% saline is not recommended due to additional expense and complexity without clear evidence of incremental risk reduction.  
  - N-Acetyl Cysteine: its use is controversial and there is variable evidence regarding its renoprotective effect.  
  - A renal physician should be consulted regarding its use.
- Metformin: Patients with Type II diabetes mellitus may be taking the oral hypoglycaemic medication metformin. It is renally excreted in its active form, but with increasing renal impairment, there is a risk of lactic acidosis (a form of metabolic acidosis) due to metformin accumulation. Lactic acidosis is a medical emergency and requires urgent treatment. The risk increases with the degree of renal dysfunction and the patient's age. Therefore, patients with stable renal function and eGFR greater than 30mL/min are at low to no risk of developing lactic acidosis as a direct consequence of iodinated contrast media administration alone.  
  - After receiving iodinated contrast media, some patients may experience an acute renal impairment. This may also result in metformin accumulation and lactic acidosis. The absolute risk remains low, however there are guidelines to prevent this from occurring. Patients with an unknown recent eGFR or an eGFR less than 30 mL/min, or who are unwell or have deteriorating renal function should cease metformin for at least 48hrs from the time of the examination and an eGFR performed prior to restarting metformin. The patient should be kept well hydrated. Patients with normal renal function do not need to cease their metformin pre-procedure or re-check renal function post-procedure.
Contrast Induced Thyrotoxicosis

Thyrotoxicosis secondary to iodinated contrast material is rare but may occur in patients with abnormal thyroid function. Patients with clinical or biochemical evidence of hyperthyroidism prior to iodinated contrast media administration are at risk of developing clinical hyperthyroidism and / or acute thyrotoxicosis. 1, 8 Thyrotoxicosis generally occurs three to six weeks following iodinated contrast media administration. Patients with known or suspected hyperthyroidism (clinical or biochemical) should be tested and treated for this in consultation with the referrer or an endocrinologist prior to contrast media administration. 1

Patients who are known to have a hyperfunctioning thyroid nodule are at increased risk of thyrotoxicosis following intravenous iodinated contrast media administration, even if they have no clinical / biochemical evidence of hyperthyroidism. 8 Patients in this situation should be advised about this risk and monitored for the development of this complication in the weeks following the injection. 1

Patients who are to undergo diagnostic or therapeutic procedures involving radioisotope scanning of the thyroid will have radioisotope uptake prevented for 8 weeks following iodinated contrast media administration. 1 This risk should be considered and weighed against the benefits of iodinated contrast media administration. 1, 8

Iodinated Contrast Use in Pregnancy and Lactation

In exceptional circumstances, when contrast use is deemed necessary, iodinated contrast media may be given to the pregnant mother. The Therapeutic Goods Administration (TGA) currently categorises the safety of iodinated contrast media during pregnancy as B1 or B2. 1 Although no adverse fetal effects due to IV contrast administration during pregnancy have been proven, current guidelines recommend that all neonates should receive thyroid function testing in the first week of life where the mother has received iodinated contrast material in accordance with current standard paediatric care. 1, 9

A Japanese study has shown an increased incidence of neonatal hypothyroidism following use of oil-based iodinated contrast for hysterosalpingography prior to conception. It is unclear whether this is true for water-soluble iodinated contrast media which are more commonly used in Australia during hysterosalpingography. 10

Current guidelines have stated that cessation of breast feeding following iodinated contrast material is not required. 1, 9 The amount of contrast media excreted in breast milk is very small and the absorbed dose to the fetus even smaller. The likelihood of either direct toxicity or allergic reaction is therefore extremely low. 9

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References - Iodinated Contrast for CT Scans