



Safe use of radiographic contrast media

Kenneth R Thomson, Professor and Director of Radiology, and Dinesh K Varma, Deputy Director of Radiology and Head of Trauma and Emergency Radiology, Department of Radiology, The Alfred, Melbourne

Summary

Injection of iodinated radiographic contrast media is generally safe, however with increased use adverse events are more likely to occur. The most important adverse effects include hypersensitivity reactions, contrast-induced nephropathy and thyrotoxicosis. There is no protocol that will prevent non-IgE-mediated anaphylaxis. In patients with moderate renal dysfunction, adequate hydration and use of as little contrast media as practical is recommended. Contrast-induced nephropathy is often transient. Metformin has been associated with lactic acidosis in patients receiving contrast media. It should therefore be discontinued for 48 hours starting on the day of the contrast study. The use of alternative non-iodinated contrast agents, particularly in ultrasound and magnetic resonance, is also growing. Gadolinium magnetic resonance agents have been associated with nephrogenic fibrosing sclerosis in patients with renal dysfunction.

Key words: adverse effects, gadolinium, kidney failure, metformin.

(Aust Prescr 2010;33:19–22)

Introduction

Contrast media are widely used in imaging, usually with CT, MRI, X-ray and more recently with ultrasound. Iodinated contrast media are the most commonly used contrast agents and are helpful in differentiating between normal and pathological areas. Common indications for contrast media include inflammatory, infective or neoplastic conditions. However, intravenous contrast is only indicated when the contrast will add diagnostic value. In patients with impaired renal function, a non-contrast scan or an alternative imaging examination may provide sufficient diagnostic information.

Iodinated contrast media

Iodine-based agents are compounds of 2,4,6 tri-iodobenzoic acid. Intravascular administration of iodinated contrast media is followed by a rapid passage into the extracellular space,

water shift into the circulating volume and then excretion predominantly via the kidneys. Iodinated contrast media are classified into non-ionic and ionic. These can have high osmolality (ionic monomers) or low osmolality (ionic dimers, non-ionic monomers e.g. iopromide, and non-ionic dimers). The osmolality, viscosity and iodine content of contrast media are closely interrelated. Adverse effects increase with higher osmolality. Iodine content is not an independent indicator of adverse events. The non-ionic dimers are preferred due to lower osmolality and less chemotoxicity. However they are more viscous than non-ionic monomers, and more expensive.

Non-ionic agents

Iopamidol is a widely used non-ionic monomer which has an osmolality twice that of plasma at a concentration of 300 mg iodine/mL. Iodixanol is a non-ionic dimer and at a concentration of 300 mg iodine/mL has an osmolality approaching that of plasma (290 mOsmol/kg). Due to its higher cost, it is used selectively for examinations where osmolality may affect the examination quality (for example, cardiac CT coronary angiography and lower limb angiography for severe ischaemia).

Ionic agents

Ionic contrast media are contraindicated for intrathecal use. Only iotroxate, which binds reversibly to plasma protein promoting biliary excretion, is approved for intravenous cholangiography in Australia.

Non-iodinated contrast media

These agents are predominantly used in ultrasound (microbubble preparations) and MRI. The MRI agents such as gadolinium are paramagnetic and shorten the T1 relaxation time. They are very occasionally used in digital subtraction angiography in individuals hypersensitive to iodinated radiographic contrast media. Higher volumes are required for adequate contrast resolution.

Carbon dioxide is also used for digital subtraction angiography when iodinated contrast is contraindicated. However, it has significant technical limitations. It must not be used for angiography above the diaphragm or when there is a right-to-left shunt, to avoid cerebral ischaemic events from the bubbles.

Safety

Although contrast media are generally safe, adverse reactions do sometimes occur.

Hypersensitivity reactions

Hypersensitivity reactions to contrast media include both IgE and non-IgE-mediated anaphylaxis, with activation of mast cells, coagulation, kinin and complement mechanisms, inhibition of enzymes and platelet aggregation.¹

Mild contrast media reactions with low osmolar media occur in less than 3% of patients and consist of skin rashes, nausea, flushing or urticaria. Moderate and severe hypersensitivity reactions include bronchospasm and wheezing, angioedema, coronary artery spasm, hypotension, cardiac arrhythmia, cardiac failure and loss of consciousness. Severe contrast reactions are uncommon, occurring in less than 0.04% of non-ionic iodinated contrast injections. Mortality due to contrast media reactions is low (less than one death per 100 000 patients).^{2,3}

In the elderly, the mortality related to contrast media administration is significantly higher. Children are more sensitive to fluid volume change related to contrast administration.

Even very small doses of iodinated contrast may cause a reaction. Test injections are not recommended. The reaction may occur immediately, however delayed reactions after an hour or sometimes up to a week can also occur. These reactions (2–5%) are not due to anaphylaxis but they are possibly T cell-mediated and may consist of a maculopapular rash, urticaria and angioedema. The osmolality is strongly related to contrast media reactions. Most severe non-fatal contrast media reactions can be prevented by using low-osmolar contrast media.

Risk factors

Previous reaction to contrast media is the most important risk factor and carries a 20–60% absolute risk during subsequent exposure. Asthma increases the risk significantly, particularly the risk of bronchospasm. Beta blockers have been associated with hypersensitivity and may worsen bronchospasm. A history of multiple allergies requiring treatment increases the risk of acute reaction to iodinated contrast three- to fivefold. Vasovagal reactions can also occur during contrast media infusion.

Treatment

If a reaction occurs, infusion of the contrast media should be ceased immediately. Although mild reactions are often self-limiting and resolve without specific treatment, reactions that begin during or immediately after the injection should always be treated as the symptoms may progress. Vasovagal

reactions are treated with elevation of the lower limbs and 0.6 mg of atropine as indicated. Treat mild delayed hypersensitivity reactions with an oral antihistamine.

Reactions associated with bronchospasm and wheezing, laryngospasm and stridor or hypotension should be treated immediately with adrenaline, intravenous fluids and oxygen, in addition to antihistamines with or without hydrocortisone. Intubation may be required and supportive medications may be necessary for 2–3 days in severe cases. Intramuscular adrenaline (1:1000) is the mainstay of treatment for severe reactions and can be repeated every 5 minutes if required. The initial dose for adults is 0.25–0.5 mL for those weighing less than 50 kg and 0.5 mL for those weighing more than 50 kg. Corticosteroids are not useful in the initial management of non-IgE-mediated reactions, but are believed to prevent or reduce delayed symptoms. Most patients recover from their reactions without any long-term morbidity.⁴ Patients who have experienced severe reactions should be advised to carry a MedicAlert card. Severe reactions should be reported to the Office of Medicines Safety Monitoring (www.tga.gov.au/adr/bluecard.htm).

Patients with recurrent reactions should not be given contrast media so other modalities should be considered for investigations. However, when iodinated intravascular contrast must be given, a different and preferably lower osmolar agent should be used and premedication with corticosteroids for 24–48 hours before the procedure is widely practised.

Contrast-induced nephropathy

In this condition, renal tubular artery vasoconstriction and altered glomerular haemodynamics due to an elevated plasma oncotic pressure are caused by the contrast media. In renal insufficiency, acetylcysteine (a vasodilator and antioxidant) and fenoldopam (a vasodilator) have been studied as preventative strategies without definitive positive results.⁵

Acute renal injury is unlikely in patients who are hydrated and have normal renal function receiving contrast media less than 4 mL/kg. In patients with mild renal impairment, hydration before injecting contrast media usually prevents worsening renal function.

Alternative investigations such as non-contrast MRI, ultrasound and carbon dioxide digital subtraction angiography should be considered in patients with moderate to severe renal impairment. Dimeric non-ionic contrast media do not have an advantage over monomeric contrast media with respect to contrast-induced nephropathy.⁶

Most hospital-based radiology practices now require measurement of serum creatinine and calculation of glomerular filtration rate (GFR) before injection of contrast media. This is because renal failure is a potential factor in hospital deaths and long-term mortality of older patients with

mild renal impairment.⁷ If GFR is less than 60 mL/min/1.72m², caution is urged and patients should be adequately hydrated when iodinated contrast media or gadolinium are used.

Metformin

Metformin has been associated with several cases of renal failure and lactic acidosis in patients who have received contrast media. If contrast media causes renal failure, metformin, which is renally excreted, can reach toxic levels resulting in lactic acidosis. It is now recommended that metformin be discontinued at least 12 hours before the contrast investigation and not be resumed for a minimum of 36 hours after the procedure, and longer if the serum creatinine has not returned to baseline. Alternative methods of managing the patient's glucose levels may be required during this interval.

Reducing the risk

The most important factors in reducing contrast-induced nephropathy are:

- avoiding repeated high dose studies at short intervals
- adequate hydration by intravenous route if necessary
- using low-osmolar non-ionic contrast media
- using diluted contrast media at the lowest volume practicable
- avoiding concurrent use of drugs that may cause renal vasoconstriction (non-steroidal anti-inflammatory drugs).

In most cases, renal function returns to baseline without specific treatment. In severe cases treatment is the same as for patients with tubular necrosis from other causes.

Nephrogenic systemic fibrosis

Gadolinium-based agents are associated with nephrogenic systemic fibrosis in patients with depressed renal function.^{8,9} Most of these cases have been in people receiving high doses of gadolinium for CT or digital subtraction angiography because of known hypersensitivity to iodinated contrast.

Patients with a GFR of less than 30 mL/min are considered to be at a high risk of nephrogenic systemic fibrosis and gadolinium should be avoided completely. The risk in patients with a GFR of more than 60 mL/min receiving low doses of gadolinium (0.1 mL/kg) is negligible. The need for gadolinium studies in patients with mild renal impairment should be decided on clinical grounds.

Iodinated contrast media and the thyroid

Iodinated contrast-induced thyrotoxicosis is rare. Iodine does not have a significant effect on patients with normal thyroid function. Patients with Graves' disease and multinodular goitre are at increased risk, and those with thyrotoxicosis should not receive the contrast.

Patients with hyperthyroidism may develop a thyroid crisis

and the accuracy of thyroid function tests will be affected by intravascular contrast media. These contrast media can also affect diagnostic thyroid isotope studies for up to eight weeks. Patients with thyroid carcinoma scheduled for treatment with radioactive iodine should not receive the contrast, as it may delay treatment for eight weeks.

Contrast media extravasation

New CT angiographic techniques involve contrast media power injectors, larger volumes and higher injection rates. As a result there is a slightly higher incidence of contrast media extravasation at or near the injection site. In severe cases, there is a risk of skin loss although this is less with the low osmolar agents.

Treatment is aimed at reducing skin metabolic needs with a cold pack for 20 minutes, and increasing the absorption of the contrast media with elevation and a crepe bandage.

Conclusion

Iodinated contrast media are commonly used during imaging with various diagnostic modalities. The low osmolar, non-ionic monomer contrast agents have a very low risk of serious reactions. Patients should be carefully evaluated for risk factors, including any history of previous reactions to contrast media, asthma, concurrent medical conditions with particular emphasis on renal and thyroid function, and current medications particularly metformin and beta blockers. Severe hypersensitivity reactions must be treated promptly like any other anaphylactic reactions with intramuscular adrenaline.

References

1. Katelaris CH, Smith WB. 'Iodine allergy' label is misleading. *Aust Prescr* 2009;32:125-8.
2. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990;175:621-8.
3. Caro JJ, Trindade E, McGregor M. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. *AJR Am J Roentgenol* 1991;156:825-32.
4. Wang CL, Cohan RH, Ellis JH, Caoili EM, Wang G, Francis IR. Frequency, outcome, and appropriateness of treatment of nonionic iodinated contrast media reactions. *AJR Am J Roentgenol* 2008;191:409-15.
5. Briguori C, Airolidi F, D'Andrea D, Bonizzoni E, Morici N, Focaccio A, et al. Renal insufficiency following contrast media administration trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation* 2007;115:1211-7.
6. Carraro M, Malalan F, Antonione R, Stacul F, Cova M, Petz S, et al. Effects of a dimeric vs a monomeric nonionic contrast medium on renal function in patients with mild to moderate renal insufficiency: a double-blind, randomized clinical trial. *Eur Radiol* 1998;8:144-7.

7. Mathew TH, Johnson DW, Jones GR; Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: revised recommendations. *Med J Aust* 2007;187:459-63.
8. Chrysochou C, Buckley DL, Dark P, Cowie A, Kalra PA. Gadolinium-enhanced magnetic resonance imaging for renovascular disease and nephrogenic systemic fibrosis: critical review of the literature and UK experience. *J Magn Reson Imaging* 2009;29:887-94.
9. MRI scans with gadolinium-containing contrast agents and the risk of nephrogenic systemic fibrosis – caution in patients with renal impairment. *Aust Adv Drug React Bull* 2008;27:2.

Conflict of interest: none declared

There is a Comment for consumers online with this article at www.australianprescriber.com/magazine/33/1/19/22

Self-test questions

The following statements are either true or false (answers on page 27)

3. Reactions to contrast media may occur up to a week after the procedure.
4. Patients with renal impairment should not take metformin when receiving contrast media.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Ambrisentan

Volibris (GlaxoSmithKline)

5 mg and 10 mg film-coated tablets

Approved indication: pulmonary arterial hypertension

Australian Medicines Handbook section 6.7

Pulmonary arterial hypertension may be idiopathic or be associated with other conditions such as connective tissue disease. The severity of pulmonary arterial hypertension is classified (I–IV) according to its effect on the patient's physical activity. Conventional treatment includes diuretics and warfarin, but more severe cases may need treatment with prostacyclins, such as epoprostenol, or endothelin receptor antagonists, such as bosentan and sitaxentan.

Ambrisentan is a selective antagonist of the endothelin type A receptor. This action blocks the vasoconstrictive effect of endothelin, a peptide produced by endothelial cells.

Like bosentan and sitaxentan, ambrisentan is taken orally. The tablets should not be chewed or crushed, but food does not affect bioavailability. Most of the dose is metabolised and excreted from the gut. The effective half-life is approximately nine hours. As the enzymes involved in the metabolism include cytochrome P450 3A4 and 2C19 there is a potential for drug interactions, but their clinical significance is currently unclear. Ambrisentan is not recommended for patients with liver disease, or if the patient has transaminase concentrations more than three times the upper limit of normal.

A dose-ranging study enrolled 64 patients with symptomatic pulmonary arterial hypertension despite conventional therapy. They could only walk an average of 343 metres in six minutes at the start of the study. After 12 weeks this had increased by approximately 36 metres irrespective of the dose. Pulmonary artery pressure decreased and there was less dyspnoea.¹

Ambrisentan was then compared with placebo in two trials which randomised 394 patients. At the start of the study these patients could only walk an average of 340–355 metres in six minutes. One study used 5 mg or 10 mg doses. After 12 weeks these doses had increased the distance the patients could walk by 31–51 metres more than placebo. The other trial tested 2.5 mg and 5 mg. These doses increased the distance covered in six minutes by 32–59 metres more than placebo. A group of 280 patients completed an extension of the studies. After 48 weeks of taking ambrisentan they were able to walk 39 metres further than they were able to at the start of the studies.²

Ambrisentan's adverse effects and interactions will become clearer with more widespread use. The most frequent adverse effects in the trials, occurring more often than with placebo, were peripheral oedema, nasal congestion, sinusitis, flushing and palpitations.² Fluid retention may present as decompensated heart failure. Hepatic function must be monitored at least once a month because of the risk of liver damage. Haemoglobin should also be measured regularly as anaemia can occur in 7% of patients. Ambrisentan is contraindicated in pregnancy.