CLINICAL PHARMACOLOGY

RISKS OF USING IODINATED CONTRAST MATERIAL FOR RADIOLOGICAL INVESTIGATIONS

Intravenous iodine-containing contrast material is used to enhance imaging during CT scanning, urological investigations and angiography. These agents can be divided into high- and low-osmolar groups; or alternately, ionic or non-ionic media. The low-osmolar agents are almost all non-ionic and are reported to have better adverse effect profiles. High-osmolar agents are usually ionic agents, although one ionic agent (sodium and meglumine ioxaglate/ Hexabrix) is relatively low-osmolar by virtue of its dimeric ring. Contrast media contribute greatly to diagnostic value, but there are some important risks associated with their use, particularly nephrotoxicity and hypersensitivity reactions. Recognition and pre-treatment of high-risk patients is important for the prevention of nephrotoxicity and, similarly, awareness, prophylaxis and immediate treatment of hypersensitivity reactions are essential.

Although radiological investigations requiring contrast administration are often carried out by specialist radiologists, it is commonly the general practitioner who requests the investigation. It is therefore important that the general practitioner is aware of the attendant risks to the patient and balances these against the benefits when requesting a particular investigation. Insight into the risks also better allows the practitioner to inform the patient about the procedure. When there is uncertainty about the best radiological investigation for a clinical problem, the case should be discussed with a radiologist.

Nephrotoxicity

This is a major concern when administering contrast. More than 90% of the dose of contrast is excreted by the kidneys within 24 hours, in patients with normal renal function. The high-osmolar agents are more likely to cause nephrotoxicity, but both types of contrast material are implicated. This is thought to arise by direct cytotoxic action on tubular epithelial cells, disturbances in renal perfusion and the generation of oxygen-free radicals, in combination with reduced activity of antioxidant enzymes in the renal cortex.

Contrast-induced nephropathy (CIN) is defined as a rise in serum creatinine of more than 44 µmol/l, or of 25% from baseline value, within 48 hours of contrast exposure in the absence of other causes of acute renal dysfunction. CIN is said to occur in 0.6 - 2.3% of the population and 1- 20% of hospitalised patients, the broad range reflecting the fact that certain subsets of patients are at a much greater risk (Table I).

Most cases of CIN are transient, with a return to baseline or near-baseline renal function within 7 - 10 days. However, up to 30% of patients who develop CIN will have a permanent decline in renal function. It is estimated that 0.7% of patients with a history of renal impairment prior to angiography will require short-term dialysis after the procedure. Furthermore, the development of CIN after coronary angiography in patients with pre-existing renal impairment has been shown to correlate with higher in-hospital and 1-year mortality rates.

Table I. **Characteristics of patients at increased risk of developing contrast-induced nephropathy**

- Pre-existing renal disease
- Diabetes mellitus
- Dehydration
- Concurrent use of nephrotoxic drugs, e.g. aminoglycosides, NSAIDs
- Advanced age
- Multiple myeloma

Prevention of contrast-induced nephropathy

Dehydration is a major risk factor for CIN and therefore attention to fluid management is extremely important in the prevention of nephropathy. Fluids are often given intravenously or orally before and after the procedure. Adequate hydration status has been found to be protective.

Various drugs have also been used in an effort to prevent the development of CIN. Furosemide, calcium-channel blockers and dopamine have been tried, but the evidence of benefit is lacking for these interventions. N-acetylcysteine (NAC) has been studied more recently. Acetylcysteine is derived from the naturally occurring amino acid, L-cysteine. NAC is thought to work by three mechanisms: acting as an oxygen free-radical scavenger, enhancing expression of nitric oxide synthase and potentiating the effect of nitric oxide. Oxygen free-radicals are directly toxic to the kidney. Nitric oxide is a potent vasodilator and increases renal blood flow.

NAC is generally used orally in 12 hourly doses on the day before and on the day of angiography. Oral use of NAC is generally well tolerated, although vomiting may occur.

Anaphylactoid reactions to oral NAC are rare and more likely to occur with intravenous use.

A meta-analysis of 13 placebo-controlled trials of NAC used during coronary angiography involving 1 892 patients has recently been published. One limitation of the meta-analysis was the fact that five different dose regimens were used in the trials.

The individual trials yielded conflicting results, but the pooled risk ratio for development of CIN was 0.68 (95% confidence intervals 0.46 - 1.01), showing a benefit which just failed to reach statistical significance.

Diabetics and any patients with renal impairment are considered to have a 5-10-fold increased risk of nephropathy. Special attention should therefore be paid to the preparation of such patients. In addition to adequate hydration, the use of NAC should be considered in high-risk patients as it is well tolerated and probably beneficial. Procedural factors such as use of a low-osmolar contrast agent and ensuring adequate time between sequential angiographic investigations are also relevant. Follow-up creatinine estimations at 48 hours are important in the at-risk patient.

'Hypersensitivity' reactions

These anaphylactoid reactions vary in severity from potentially life-threatening to minor. These usually occur within 5 - 10 minutes of contrast exposure, but may manifest hours later. Multiple organ systems may be affected (see Table II).

The risk of developing any hypersensitivity reaction is 4 - 12% for high-osmolar agents and 1- 3% for the low-osmolar (non-ionic) contrast media. The risk of a severe reaction is 0.16% for ionic media and 0.03% with the non-ionic media.

These reactions are idiosyncratic. Adverse events of this nature may develop in patients who have not been exposed to contrast before. IgE has not been implicated in the pathogenesis, suggesting that it is not a true allergic reaction.

It is important to remember that skin rashes may present days after contrast administration.

Patients at increased risk of experiencing hypersensitivity reactions

Patients with a history of allergy or asthma have an increased risk of developing hypersensitivity reactions. Most guidelines suggest that asthmatics should be given contrast media with caution. A previous hypersensitivity reaction to contrast is a relative contraindication to contrast administration, balancing the risk against possible diagnostic information. Alternative imaging not requiring iodinated contrast should always be considered. Pretreatment with steroids and antihistamines is used to reduce the risk.

Management of these hypersensitivity reactions requires vigilance and readiness to administer emergency treatment. An emergency cart should be nearby whenever contrast is administered. Adrenaline, intravenous hydrocortisone and antihistamines are key agents that can be used. Airway management and other resuscitative measures are also important.

Other adverse reactions

Nausea, vomiting, a metallic taste in the mouth, flushing and abdominal pain are common. These usually resolve spontaneously and are dose-dependent. It is important to remember that these may occur 30 minutes or more after administration of contrast, emphasising the importance of monitoring the patient even after the investigation has been completed.

Local reactions to contrast include tissue damage by increased compartment pressure (and possibly minor direct toxicity) when large-volume (50 ml or more) extravasations occur. Vascular pain, venous thrombosis in the arm, inflammatory cellulitis and skin necrosis have also been described.

The use of iodine-containing contrast material has occasionally been associated with hyperthyroidism and hypothyroidism due to the small amount of free iodine that may be present. Patients with isolated suppressed TSH and minimal autonomous tissue can probably safely be given iodinated

Table II. **'Hypersensitivity' reactions to contrast, by organ system**

Cardiovascular system	Respiratory system	Central nervous system	Skin
Shock and hypotension Tachy- or bradycardia Ventricular fibrillation	Bronchospasm Adult respiratory distress syndrome	Convulsions	Urticaria Angioedema Stevens-Johnson syndrome Fixed drug eruption Bullous lichen planus

contrast. The risk appears to be significant only for those patients with clinical hyperthyroidism.

Contrast material should be avoided in pregnancy if possible as it crosses the placenta, and safety in pregnancy has not been proven. Neonatal hypothyroidism has occurred following exposure. Breastfeeding should be discontinued for 24 hours following exposure.

Other rare adverse effects include parotid swelling (iodine mumps of iodism), sometimes up to 2 - 4 days after contrast exposure and thrombotic thrombocytopenic purpura.

Problems related to the concurrent use of contrast and other drugs

Metformin. Metformin-associated lactic acidosis has been reported in patients given radiological contrast. However, 17 of 18 cases reviewed by McCartney *et al*. had underlying renal dysfunction prior to contrast use, which itself is a contraindication to metformin therapy. It is postulated that the acute insult to a vulnerable kidney may delay the renal clearance of metformin, its main mode of elimination. This predisposes the patient to lactic acidosis caused by metformin. The Royal College of Radiologists initially advised that metformin should not be taken 48 hours *before* or after IV contrast, and should only be recommenced if serum creatinine remains normal or normalises. However, this has been revised to allow metformin to be stopped at the time of contrast administration, and only recommenced once the renal function is re-evaluated and shown to be normal.

Nephrotoxic drugs such as the aminoglycosides and non-steroidal anti-inflammatory drugs may increase the risk of development of CIN.

Angiotensin converting enzyme inhibitors. Some guidelines suggest that the use of an ACE-inhibitor prior to contrast may increase the risk of CIN. The proposed mechanism is a disturbance of the regulation of perfusion of the kidney caused by the drug. However, the evidence is conflicting and ACE-inhibitors have also been promoted to prevent CIN.

Further reading

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SINGLE SUTURE

WOMEN GET ANGINA

Angina is generally thought to be more common in men than in women, but a recent study in Finland of more than 100 000 people with angina, aged between 45 and 89, showed it to be equally common in both. And to make matters worse, women are more likely than men to be told that their symptoms are stress-related and not cardiac in origin and so are not tested for underlying heart disease. On top of this, these women were more likely to die of heart disease than men and women who were tested. The authors point out that while women may be relatively protected from heart attack, they are not protected from angina, and so need fair access to treatment and investigation.

Hemingway H, *et al. JAMA* 2006; **295:** 1404.