



# Risks of Iodinated Contrast Media - What You Should Know

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## Introduction

Diagnostic and interventional procedures using contrast media are performed with increasing frequency. The patient population subjected to these procedures is progressively older and has more comorbid conditions. Therefore contrast media continue to cause concern among patients, referring clinicians, and radiologists because of their widespread use and the rare but potentially important adverse events.

Adverse events due to contrast media can be categorised into renal or non-renal adverse reactions.

## Renal adverse reactions

Contrast media-induced nephropathy is defined as impairment in renal function (an increase in serum creatinine by >25% or 44  $\mu\text{mol/L}$  (0.5mg/dL) occurring within 3 days following the intravascular administration of contrast media in the absence of an alternative etiology<sup>1</sup>.

Risk factors include raised s-creatinine levels particularly secondary to diabetic nephropathy, dehydration, congestive heart failure, age over 70 years old, concurrent administration of nephrotoxic drugs, e.g., non-steroidal anti-inflammatory drugs<sup>1</sup>. Identifying patients at risk at time of referral for a contrast-enhanced imaging examination is crucial. The referring clinician should ask the patient for history of: renal disease, renal surgery, proteinuria, diabetes mellitus, hypertension, gout, and recent intake of nephrotoxic drugs<sup>2</sup>. Recent serum creatinine preferably within the preceding month for high-risk patients should be provided with the imaging request<sup>3</sup>.

Several measures have been recommended to reduce the incidence of contrast medium-induced nephropathy. Extracellular volume expansion and the use of low-osmolar contrast media have been found to be most systematically effective<sup>1</sup>. Adequate hydration in terms of oral fluid intake or intravenous normal saline (depending on the clinical situation) at least 100 ml per hour starting 4 hours before to 24 hours after contrast administration is recommended. Concurrent administration of nephrotoxic drugs should be stopped for at least 24 hours. High osmolar contrast media, large doses of contrast media, or multiple studies with contrast media within a short period of time should be avoided. Alternative imaging techniques that do not require the administration of iodinated contrast media should be considered.

Recent work in preventing and ameliorating contrast medium-induced nephropathy with N-acetyl cysteine<sup>4,6</sup> and various hydration regimens including use of sodium bicarbonate<sup>7</sup> has been promising but is not conclusive yet. No measure has yet resulted in avoidance of its occurrence in all patients.

## Non-renal adverse reactions

These are generally classified as idiosyncratic or chemotoxic. Idiosyncratic (i.e., anaphylactoid) reactions occur unpredictably and independently of the dose and concentration of the agent. Most anaphylactic reactions relate to the release of active mediators. Conversely, chemotoxic-type effects relate to the dose, the molecular toxicity of each agent, and the physiologic characteristics of the contrast agents (i.e., osmolality, viscosity, hydrophilicity, calcium-binding properties, and sodium content). Chemotoxic-type effects are more likely in patients who are debilitated or medically unstable<sup>8</sup>.

Acute reactions to contrast media can be divided into minor, intermediate, and severe life-threatening. Minor reactions include flushing, nausea, arm pain, pruritus, vomiting, headache, and mild urticaria. Such reactions are usually mild in severity, of short duration, self-limiting and generally require no specific treatment. Intermediate reactions are more serious degrees of the same symptoms, moderate degrees of hypotension, and bronchospasm. The reactions usually respond readily to appropriate therapy. Severe life-threatening reactions include severe manifestations of all the symptoms described as minor and intermediate reactions, plus convulsions, unconsciousness, laryngeal oedema, severe bronchospasm, pulmonary oedema, severe cardiac dysrhythmias and arrest, cardiovascular and pulmonary collapse. The prevalence of adverse reactions with low-osmolar contrast media is less than with high-osmolar contrast media by a factor of 5-6<sup>9</sup>. Lethal reactions rarely occur. The actual risk of death is less than one in 130,000 at most<sup>9</sup>.

The incidence of severe adverse reactions increases in patients with previous contrast medium reaction, bronchial asthma and allergy requiring medical treatment. Premedication with corticosteroid prophylaxis has been proved safe and effective in preventing minor adverse events in high-risk patients when ionic agents are used<sup>10</sup>. The data indicating a protective effect of corticosteroid prophylaxis are less established when non-ionic agents are used. Opinion is divided about the value of premedication when non-ionic agents are used. Even if it is given, there is a wide



variety of regimes with different doses, number of doses, and frequency for corticosteroid prophylaxis<sup>11</sup>.

The usual recommended regime of corticosteroid prophylaxis is as follows: Prednisolone 30mg orally or Methylprednisolone 32mg orally 12 and 2 hours before contrast medium<sup>11</sup>. Corticosteroids are not effective if given less than 6 hours before contrast medium. Antihistamines H1 and H2 may be used in addition to corticosteroids, but opinion is divided.

## Late Adverse Reactions

Late adverse reactions to intravascular iodinated contrast media are defined as reactions occurring 1 hour to 1 week after injection. The prevalence remains uncertain and the pathophysiology is not fully understood<sup>12</sup>. A variety of symptoms (e.g. nausea, vomiting, headache, itching, skin rash, musculoskeletal pains, fever) have been described, but many are unrelated to the contrast medium. Allergy-like skin reactions are well-documented side effects of contrast media, with an incidence of approximately 2%. Most late skin reactions after contrast medium exposure are probably T-cell-mediated allergic reactions. Patients at increased risks are those with history of previous contrast medium reaction and those undergoing interleukin-2 treatment. Most skin reactions are usually mild to moderate, self-limiting and likely resolve within a week. Treatment is symptomatic and similar to the treatment of other drug-induced skin reactions.

## Contrast extravasation

Extravasation of contrast material is a well-recognised complication. The introduction of automated power injection has increased the incidence because power injection may result in extravasation of large volumes in a short period of time and may lead to severe tissue damage<sup>13</sup>. Infants, young children, unconscious and debilitated patients are particularly at risk of extravasation during contrast media injection. Fortunately most extravasations result in minimal swelling or erythema and have no long-term sequelae. Occasionally severe skin ulceration, soft tissue necrosis, and compartment syndrome may occur. Conservative treatment with use of ice packs, limb elevation and careful monitoring is adequate in most cases. If a serious injury is suspected, the advice of a surgeon should be sought.

## Effects of iodinated contrast media on thyroid function in adults

Patients with Grave's disease, multinodular goitre and thyroid autonomy are at risk of development of thyrotoxicosis after administration of iodinated contrast media. Iodinated contrast media should not be given to patients with manifest hyperthyroidism<sup>14</sup>. Patients undergoing therapy with radioactive iodine should not have received iodinated contrast media for at least two months before treatment. Isotope imaging of thyroid should be avoided for two months after iodinated contrast medium injection.

## The use of contrast media during pregnancy and lactation

There is no evidence suggesting that iodinated contrast media are teratogenic in humans. On the other hand, the experience is too limited to conclude that they are safe. It is therefore wise to avoid administering them in women who are pregnant (particularly in the first trimester) when possible<sup>15</sup>. In exceptional circumstances when radiographic examination is essential, iodinated contrast media may be given to the pregnant women. The risks must be balanced against the possible benefits. Following administration of iodinated agents to the mother during pregnancy, thyroid function should be checked in the neonate during the first week<sup>16</sup>. Overall, the theoretical risks of radiation exposure are most likely greater than those incurred from contrast media.

There is no real evidence of contrast agent-induced toxicity in newborns, but on the other hand there are little concrete data confirming the safety of these medications in infants. The consensus recommendation is that a breast-feeding mother should use a pump to remove breast milk before contrast agent administration, and then afterward, she should use the pump and discard breast milk for 12-24 hours before resuming normal breast-feeding<sup>15</sup>. Since the biological half-life of iodinated contrast agents is less than 60 minutes, the amount remaining in the mother (assuming her renal function is normal) after 12 hours is essentially undetectable<sup>15</sup>.

## Effects of iodinated contrast media on blood and endothelium

All iodinated contrast media have anticoagulant properties<sup>17</sup>. This effect is greater with ionic contrast media. Several of the *in vitro* and experimental *in vivo* studies on haematological effects of contrast media have not been confirmed by clinical studies. Low- or iso-osmolar contrast media should be used for diagnostic and interventional angiographic procedures, including phlebography. Meticulous angiographic technique is the most important factor for reducing the thrombotic complications associated with angiographic procedures. Drugs and interventional devices that decrease the risk of thromboembolic complications during interventional procedures minimise the importance of the effects of contrast media.

## Conclusions

Despite new formulations and improved safety, iodinated contrast media are not without risk. The pathophysiology is not fully understood yet. Prevention with early identification of patients at risk at time of referral for a contrast-enhanced imaging examination is crucial. The risks must be balanced against the possible benefits. Alternative imaging techniques that do not require the administration of iodinated contrast media should be considered. If contrast medium is to be given to high-risk patients, precaution with adequate hydration and use of low osmolar contrast media, attention with prompt treatment to whenever any adverse events are the key strategies.



## References

- Morcos SK, Thomsen HS, Webb JAW, and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR). Contrast-media-induced nephrotoxicity: a consensus report. *Eur Radiol* 1999;9:1602-1613.
- Thomsen HS, Morcos SK, and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR). In which patients should serum-creatinine be measured before contrast medium administration? *Eur Radiol* 2005;15(4):749-54.
- Gleeson TG, Bulugahapitiya S, Contrast-induced nephropathy. *AJR* 2004;183(6):1673-89.
- Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000;343:180-184.
- Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). *Am J Cardiol* 2002;89:356-358.
- Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA* 2003;289:535-558.
- Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 2004;291:2328-2334.
- Thomsen HS. Guidelines for contrast media from the European Society of Urogenital Radiology. *AJR* 2003;181(6):1463-71.
- 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;175:621-628.
- Lasser EC, Berry CC, Talner LB, et al. Pre-treatment with corticosteroids to alleviate reactions to intravenous contrast material. *N Engl J Med* 1987;317:845-849.
- Morcos SK, Thomsen HS, Webb JAW, and members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR). Prevention of generalized reactions to contrast media: a consensus report and guidelines. *Eur Radiol*. 2001;11(9):1720-8.
- Webb JA, Stacul F, Thomsen HS, Morcos SK, and members Of The Contrast Media Safety Committee Of The European Society Of Urogenital Radiology (ESUR). Late adverse reactions to intravascular iodinated contrast media. *Eur Radiol*. 2003 Jan;13(1):181-4.
- Bellin MF, Jakobsen JA, Tomassin I, Thomsen HS, Morcos SK, and members of Contrast Media Safety Committee Of The European Society Of Urogenital Radiology. Contrast medium extravasation injury: guidelines for prevention and management. *Eur Radiol*. 2002 Nov;12(11):2807-12.
- van der Mollen AJ, Thomsen HS, Morcos SK, and members of the Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). Effect of iodinated contrast media on thyroid function in adults. *Eur Radiol*. 2004 May;14(5):902-7.
- American College of Radiology Committee on Drugs and Contrast Media. Manual on contrast media. 5<sup>th</sup> ed. Reston, Va: American College of Radiology, 2004.
- Webb JA, Thomsen HS, Morcos SK and members of Contrast Media Safety Committee of European Society of Urogenital Radiology (ESUR). The use of iodinated and gadolinium contrast media during pregnancy and lactation. *Eur Radiol*. 2005 Jun;15(6):1234-40.
- Aspelin P, Stacul F, Thomsen HS, Morcos SK, van der Molen AJ; Members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR). Effects of iodinated contrast media on blood and endothelium. *Eur Radiol*. 2006 Jan 5;1-9.