

Contrast media-induced nephropathy: risk assessment and reduction

Key words: contrast media, comparative studies; contrast media, toxicity; kidney, effects of drug on; kidney, failure

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Abstract

Contrast media-induced nephropathy (CIN) is a problem that is often under-recognised in clinical practice. The renal impairment is usually temporary, but in some patients acute renal failure can develop and dialysis may be necessary. Several independent patient-related and contrast-related risk factors contribute to the likelihood of CIN. Patients with both diabetes and pre-existing renal impairment are at the highest risk. Practices to identify patients at risk vary: it may be possible to identify patients who may be at risk using screening questionnaires. The prevalence of CIN correlates with contrast media (CM) dose: therefore the amount of CM has to be minimised in at-risk patients. Non-ionic monomers (low osmolar CM) are beneficial in comparison with ionic monomers (high osmolar CM) in patients with pre-existing renal impairment. Encouraging results have been obtained recently with a non-ionic, dimeric, isosmolar compound, iodixanol, possibly underscoring the relationship between lower CM osmolality and lower nephrotoxicity. Adequate hydration is recommended in at-risk patients. Various drugs that have been used in attempts to prevent CIN have provided contradictory results in clinical trials and therefore their effectiveness remains to be proven.

Introduction

The use of iodinated contrast media (CM) in diagnostic and interventional procedures has increased greatly over the past 30 years, with an estimated 60 million doses applied worldwide each year. Increasing numbers of patients who may be at risk of contrast media-induced nephropathy (CIN) are being referred for procedures requiring the use of CM.

Contrast media-induced nephropathy is typically defined as an impairment of renal function characterised by an increase in serum creatinine of more than 25% or 0.5 mg/dL (44 µmol/L) over baseline, occurring within three days of the administration of CM, in the absence of an alternative aetiology. An agreement on this definition is extremely important to allow comparisons between different

trials. This definition of CIN was adopted by the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR) in 1999.¹ The reported prevalence of CIN actually varies, according to definition and patient group, from <5% where there are no risk factors up to 50% in patients at high risk. The ESUR tried to reach a consensus on prevalence by disseminating a questionnaire to both experts and members of the Society.¹

PREVALENCE OF CIN ESUR CONSENSUS

Low in patients without risk factors, <5%

Prevalence in patients with risk factors	Members (%)	'Experts' (%)
10–20%	63	35
20–30%	19	41
>30%	19	24

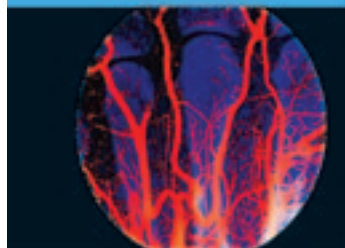
After Morcos *et al*, 1999¹

In clinical practice, the prevalence of CIN may be underestimated because serum creatinine is a comparatively insensitive measure of renal function in patients without kidney disease and, furthermore, patients do not always undergo renal function tests prior to, and seldom following, procedures.

Despite the shift from high osmolar CM to the less nephrotoxic low osmolar agents, CIN remains a significant problem in certain patient groups. It is associated with increased morbidity and mortality^{2,3} and is one of the most costly to treat adverse reactions to CM.⁴

At-risk patients

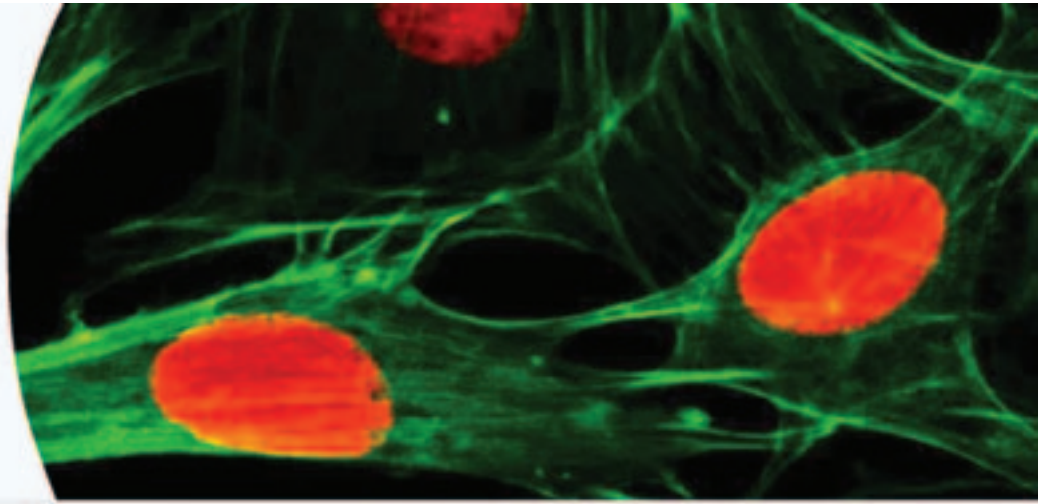
The clinical burden of CIN can be minimised by identifying at-risk patients. Several independent patient-related and procedure-related risk factors contribute to the likelihood and extent of CIN. The most important patient-related risk factor is pre-existing renal impairment, increasing the risk of CIN more than 20-fold.⁵ The risk of CIN increases exponentially in



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relation to baseline serum creatinine above a baseline of 106 $\mu\text{mol/L}$.⁶ It is questionable whether diabetes mellitus is actually an independent risk factor.^{1,2,5,7,8} However, there is general agreement that patients with both diabetes and pre-existing renal impairment are at highest risk. In one study CIN occurred in 0.6% of patients with diabetes and normal renal function, in 5.7% of patients with renal insufficiency alone and in 19.7% of patients with diabetes and renal insufficiency.⁵ In another study, 50% of patients with diabetic nephropathy and creatinine clearance below 30 mL/min showed a rise of at least 25% in serum creatinine and 15% required dialysis.⁹ Other possible patient-related risk factors include dehydration, old age (with a questionable threshold), congestive heart failure, history of CIN and concurrent administration of nephrotoxic drugs.

PATIENT-RELATED RISK FACTORS

- Pre-existing renal impairment with diabetes mellitus
- Pre-existing renal impairment without diabetes mellitus
- Dehydration
- Congestive heart failure
- Old age
- Concurrent administration of nephrotoxic drugs (NSAIDs, aminoglycosides)

Potential patient-related risk factors include multiple myeloma, hypertension, hyperuricaemia, proteinuria and male gender. However, these are not usually considered as independent predictors of CIN nowadays.^{1,10}

Identifying at-risk patients

Renal insufficiency, the greatest single risk factor for CIN, may not be apparent until it is quite advanced. The practice of measuring serum creatinine before administration of CM is variable.¹¹ A survey in the USA by Lee *et al.* found that serum creatinine was assessed before urography, body CT and head CT in 13%, 20% and 14% of institutions, respectively. In institutions where routine serum creatinine measurement was not required, about 60% requested a measurement in patients with diabetes.¹¹

Routine measurement of serum creatinine in every patient before administration of contrast is not always practical or possible.¹² In addition, obtaining pre-injection serum creatinine values in all patients is expensive, and probably not cost-effective given the low risk of renal damage in the general patient population.¹¹

It may be possible to identify patients with low risk of underlying renal insufficiency, in whom serum creatinine testing is not essential, by evaluating risk factors.^{12,13} Olsen & Salomon found that a study form evaluating historical risk factors completed by physicians in the emergency department identified about 99% of patients who proved to have abnormally high serum creatinine;¹³ this approach is thus associated with a low possibility of failing to identify a patient with renal impairment. Similarly, Choyke *et al.* found that a six-question questionnaire, completed by patients, had the potential to identify 94% of patients with normal serum creatinine and 99% of patients with serum creatinine below 1.7 mg/dL, the cut-off for iodinated CM in their institution.¹² These authors concluded that the questionnaire could reduce routine serum creatinine determination by 67%, reducing costs, decreasing delays and increasing patient satisfaction.

There is also variability in how a serum creatinine level, once obtained, is interpreted.¹¹ In the survey by Lee *et al.*, the mean cut-off value above which contrast was not given was 2.1 mg/dL, but the standard deviation was fairly broad; the cut-off values cited ranged from 1.4 mg/dL to >2.6 mg/dL.¹¹ Interestingly, the presence of risk factors appeared to reduce the cut-off value only slightly, to a mean of 1.9 mg/dL. Dose of CM given is influenced by serum creatinine levels.¹



Contrast media-induced nephropathy: risk assessment and reduction *continued*

Fulvio Stacul

Serum creatinine is a relatively crude measure of glomerular filtration rate, and it has been suggested that creatinine clearance, calculated or measured, should be used to identify at-risk patients as it provides a better indication of renal function.¹⁴ Creatinine clearance can be calculated according to the formula $[(140 - \text{age}) \times \text{weight}] \div [\text{serum creatinine (mg/dL)} \times 72]$ (with the value for females being 0.85 times the value calculated with this formula). In a study of 1826 patients who underwent coronary intervention, no patient with a calculated creatinine clearance above 47 mL/min developed acute renal failure requiring dialysis.²

Which contrast and how much?

Contrast media-related risk factors include contrast dose, contrast osmolality, previous CM injection and route of administration of CM (intra-arterial administration carries higher risks).

CM-RELATED RISK FACTORS

- CM dose
- Type of CM
- Multiple administrations of CM
- Intra-arterial administration of CM

The prevalence of CIN correlates with dose. In one large series, the cut-off dose of CM below which there was no CIN requiring dialysis was 100 mL.² Other authors have reported a threshold effect related to renal function.^{15,16} The consensus cut-off dose derived from the ESUR questionnaire with a 300 mgI/mL contrast agent was 400 mL in patients with normal serum creatinine, 150 mL in patients with serum creatinine levels between 130 and 300 $\mu\text{mol/mL}$ and 60–100 mL in patients with higher serum creatinine levels.¹

A meta-analysis from 25 trials of the relative nephrotoxicity of high and low osmolar CM showed that the use of low-osmolality agents is beneficial in patients with existing renal failure.¹⁷ These data were validated by a later report that demonstrated that a non-ionic monomeric (low osmolar) CM (iohexol) was significantly less nephrotoxic than an ionic monomer

(diatrizoate, a high osmolar CM) in patients with pre-existing renal insufficiency alone or combined with diabetes undergoing cardiac angiography.⁵ Among patients with renal insufficiency alone, CIN developed in 4.1% following administration of iohexol and in 7.4% following injection of diatrizoate. The prevalence increased to 11.8% and 27.0% respectively in patients with pre-existing renal insufficiency combined with diabetes.

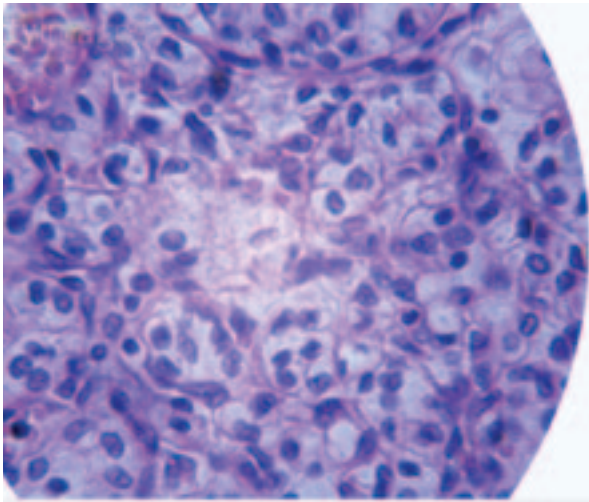
Very recently, the results from a study comparing the nephrotoxic effects of a non-ionic, dimeric, isosmolar CM, iodixanol, with those of iohexol in 129 patients with diabetes and renal impairment (serum creatinine 1.5–3.5 mg/dL) undergoing coronary or aortofemoral angiography have been reported by Aspelin *et al.*¹⁸

CIN IN PATIENTS WITH DIABETES AND RENAL IMPAIRMENT UNDERGOING ANGIOGRAPHY (n=129)

	IODIXANOL	IOHEXOL	p
Peak increase SCr day 0-3 (mg/dL)	0.13	0.55	0.001
Change in SCr day 0-7 (mg/dL)	0.07	0.24	0.003
Peak SCr \geq 44.2 mmol/L (% pts)	3	26	0.002
Peak SCr \geq 88.4 mmol/L (% pts)	0	15	

After Aspelin *et al.*, 2003¹⁸
SCr, serum creatinine

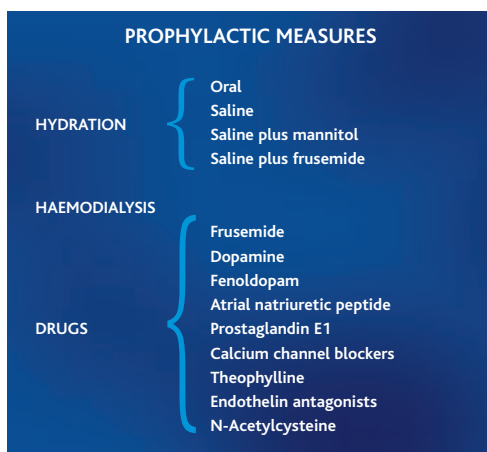
An increase in serum creatinine of ≥ 0.5 mg/dL was reported in 3% of the patients who received iodixanol in comparison with 26% of the patients who were injected with iohexol ($p=0.002$), while an increase in serum creatinine of 1.0 mg/dL or more was reported in 0% and 15% of the patients, respectively ($p=0.003$). The odds of nephropathy appeared to be 11 times higher with iohexol than with iodixanol. The reported prevalence of CIN following iohexol administration (26%) was consistent with the results of previous studies testing non-ionic monomers in patients with renal impairment, while the prevalence after iodixanol administration was very low (3%), much better than in any other clinical study in this type of patient using low osmolar agents alone.



Previous clinical trials in at-risk patients had failed to show significant differences between iodixanol and non-ionic monomers, or revealed a slight advantage of the dimer.¹⁹⁻²¹ It is possible that the lower number of patients enrolled in the previous trials and, above all, the association of renal impairment and diabetes in the population investigated by Aspelin *et al.* explain these different results.¹⁸ The magnitude of the difference between the two agents is surprising, and could highly favour the use of iodixanol in this patient group. Additional clinical studies, to further validate these results and to evaluate outcomes in other groups of at-risk patients with different procedures, are warranted.

Prevention: is it possible?

Possible prophylactic measures for preventing CIN have been investigated in many clinical trials.



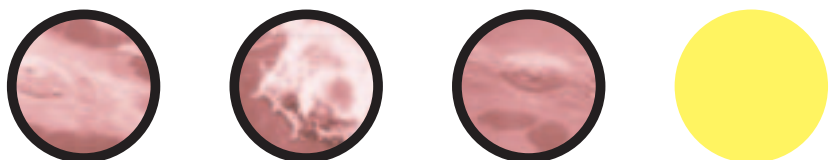
However, only hydration is widely accepted and used in clinical practice. Isotonic hydration was more effective than half-isotonic hydration in 1620 patients who underwent cardiac angiography.²² The best route of administration (oral or intravenous) is questionable. According to the guidelines of the ESUR¹ at least 100 mL per hour should be given (orally or intravenously), beginning 4 hours before and continuing until 24 hours after CM administration; in hot climates the fluid volume must be increased.

Haemodialysis following CM administration has been proven not to offer any protection against CIN, possibly because of the very rapid onset of renal injury after CM injection. Therefore, it is no longer recommended.²³

The effectiveness of different drugs tested for prophylaxis has not been fully proven: some have not proven beneficial, some have provided contradictory results in different trials, and others are still in an early experimental phase.^{1,24-26} Diuretics such as frusemide did not provide any protection and may actually be deleterious.²⁷ Among the large number of vasodilators that have been tested, dopamine and atrial natriuretic peptide did not offer protection in patients with diabetic nephropathy, who actually showed an increased rate of CIN.²⁸

Fenoldopam, a selective dopamine-1 receptor agonist, is a promising drug, but clinical experience with it is very limited and the administration of this drug has significant disadvantages. Prostaglandin E1 proved beneficial in one clinical trial in patients with chronic renal failure but the side effects of this drug may limit its clinical use.²⁹ Both theophylline and calcium channel blockers gave conflicting results in clinical trials.^{30,31} However, the different dosages and administration routes make comparison among the trials difficult and the utility of these agents remains contentious. Contradictory results have also been obtained with endothelin antagonists.

Recently, *N*-acetylcysteine has received much attention. This drug has several advantages, namely its low cost, general availability, ease of administration and limited side effects, that possibly justify its rather extensive use in clinical practice despite contradictory results on its efficacy from different clinical trials.³²⁻³⁶



Contrast media-induced nephropathy: risk assessment and reduction *continued*

Fulvio Stacul

Conclusions

Contrast media-induced nephropathy is a problem that is often under-recognised in clinical practice. It is costly, prolonging hospitalisation and potentially necessitating dialysis. The burden of CIN could be reduced by identifying at-risk patients. In these patients adequate hydration is required, the administration of nephrotoxic drugs should be stopped for at least 24 hours, the contrast dose should be minimised and contrast agents with a more favourable renal profile are recommended.

What we knew before and what this tells us

- CIN has received much attention in the literature, but many uncertainties still exist
- A widely accepted definition of CIN is essential to permit comparisons between clinical trials
- Patients considered to be at risk are well established in the literature, but the threshold CM dose in these patients is based more on perceptions than on scientific data
- The use of drugs to prevent CIN is matter for debate; no drug has been fully proven to be effective to date
- Iodixanol showed surprisingly low nephrotoxicity in a group of high-risk patients but additional clinical studies to validate these results are warranted

References

1. Morcos SK, Thomsen HS, Webb JA, et al. Contrast-media-induced nephrotoxicity: a consensus report. *Eur Radiol* 1999;**9**:1602–13.
2. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 1997;**103**:368–75.
3. Gruberg L, Mintz GS, Mehran R, et al. The prognostic implications of further renal function deterioration within 48h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. *JACC* 2000;**36**:1542–8.
4. Powe NR, Moore RD, Steinberg EP. Adverse reactions to contrast media: factors that determine the cost of treatment. *Am J Roentgenol* 1993;**161**:1089–95.
5. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. *Kidney Int* 1995;**47**:254–61.
6. Davidson CJ, Hlatky M, Morris KG, et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective study. *Ann Intern Med* 1989;**110**:119–24.
7. Lautin EM, Freeman NJ, Schoenfeld AH, et al. Radiocontrast-associated renal dysfunction: incidence and risk factors. *AJR* 1991;**157**:49–58.
8. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. *N Engl J Med* 1989;**320**:143–9.
9. Manske CL, Sprafka JM, Strony JT, Wang Y. Contrast nephropathy in azotemic diabetic patients undergoing coronary angiography. *Am J Med* 1990;**89**:615–20.
10. McCarthy CS, Becker JA. Multiple myeloma and contrast media. *Radiology* 1992;**183**:519–21.
11. Lee JKT, Warshauer DM, Bush WH, et al. Determination of serum creatinine level before intravenous administration of iodinated contrast medium. A survey. *Invest Radiol* 1995;**30**:700–5.
12. Choyke PL, Cady J, DePollar SL, et al. Determination of serum creatinine prior to iodinated contrast media: is it necessary in all patients? *Tech Urol* 1998;**4**:65–9.
13. Olsen JC, Salomon B. Utility of the creatinine prior to intravenous contrast studies in the emergency department. *J Emerg Med* 1996;**14**:543–6.
14. McCullough PA, Manley HJ. Prediction and prevention of contrast nephropathy. *J Interv Cardiol* 2001;**14**:547–58.
15. Cigarroa RG, Lange RA, Williams RH, Hillis LD. Dosing of contrast material to prevent contrast nephropathy in patients with renal disease. *Am J Med* 1989;**86**:649–52.
16. Vlietstra RE, Nunn CM, Narvarte J, Browne KF. Contrast nephropathy after coronary angioplasty in chronic renal insufficiency. *Am Heart J* 1996;**132**:1049–50.
17. Barrett BJ, Carlisle EJ. Metaanalysis of the relative nephrotoxicity of high and low-osmolality iodinated contrast media. *Radiology* 1993;**188**:171–8.
18. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med* 2003;**348**:491–9.
19. Carraro M, Malalan F, Antonione R, et al. Effects of a dimeric vs monomeric non ionic 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.
20. Chalmers N, Jackson RW. Comparison of iodixanol and iohexol in renal impairment. *Br J Radiol* 1999;**72**:701–3.
21. Jakobsen JA, Berg KJ, Kjaeresgaard P, et al. Angiography with nonionic X-ray contrast media in severe chronic renal failure: renal failure and contrast retention. *Nephron* 1996;**73**:549–56.
22. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media-associated nephropathy. *Arch Intern Med* 2002;**162**:329–35.
23. Morcos SK, Thomsen HS, Webb JA, et al. Dialysis and contrast media. *Eur Radiol* 2002;**12**:3026–30.
24. Berg KJ. Nephrotoxicity related to contrast media. *Scand J Urol Nephrol* 2000;**34**:317–22.
25. Morcos SK. Contrast media-induced nephrotoxicity – questions and answers. *BJR* 1998;**71**:357–65.
26. Waybill MM, Waybill PN. Contrast media-induced nephrotoxicity: identification of patients at risk and algorithms for prevention. *J Vasc Interv Radiol* 2001;**12**:3–9.
27. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994;**331**:1416–20.
28. Weisberg LS, Kurnik PB, Kurnik BRC. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney Int* 1994;**45**:259–65.
29. Sketch MH, Whelton A, Schollmayer E, et al. Prevention of contrast media-induced renal dysfunction with prostaglandin E1: a randomized, double-blind, placebo-controlled study. *Am J Therap* 2001;**8**:155–62.
30. Carraro M, Mancini W, Artero M, et al. Dose effect of nitrendipine on urinary enzymes and microproteins following non-ionic radiocontrast administration. *Nephrol Dial Transplant* 1996;**11**:444–8.
31. Neumayer HH, Junge W, Kufner A, Wenning A. Prevention of radiocontrast-media-induced nephrotoxicity by the calcium channel blocker nitrendipine: a prospective randomised clinical trial. *Nephrol Dial Transplant* 1989;**4**:1030–6.
32. Allagaband S, Tumulari R, Malik AM, et al. Prospective randomized study of N-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. *Catheter Cardiovasc Interv* 2002;**57**:279–83.
33. Briguori C, Manganelli F, Scarpato P, et al. Acetylcysteine and contrast agent-associated nephrotoxicity. *J Am Coll Cardiol* 2002;**40**:298–303.
34. Diaz-Sandoval LJ, Kosowsky BD, Lesordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). *Am J Cardiol* 2002;**89**:356–8.
35. Durham JD, Caputo C, Dokko J, et al. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. *Kidney Int* 2002;**62**:2002–7.
36. Tepel M, van der Giet M, Schwarzfeld C, et al. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000;**343**:180–4.