

Practical issues in the prevention and treatment of contrast nephrotoxicity

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Kidney dysfunction is a serious complication that can occur following the administration of contrast media (CM). Although the incidence of contrast nephropathy (CN) is low in the general population (1 - 2%) it poses a serious risk to those with impaired kidney function. Other risks include diabetes, old age and dehydration. The first step in prevention is to identify patients at risk. In such patients a small dose of non-ionic iso-osmolar CM together with adequate hydration (preferably an intravenous infusion of 0.45% or 0.9% normal saline) and oral N-acetylcysteine (NAC) dramatically reduces CN. Although the disease occurs infrequently with normal kidney function, its frequency increases with decreasing kidney function, ranging from 5% in patients with mild kidney insufficiency to 50% in those with severe dysfunction and diabetes. Given that CN is associated with increased morbidity, mortality and prolonged hospitalisation, and possibly with long-term kidney impairment, there is great interest in its prevention.¹

Epidemiology

Although definitions may vary, a commonly accepted and applied definition is a > 25% increase in serum creatinine level that occurs within 48 hours of contrast exposure.² Once CN occurs, kidney function remains depressed for 1 - 3 weeks but returns to normal or near normal in most cases.³ The presence of predisposing risk factors (Table I) increases the risk of CN and in the elderly patient multiple risk factors may be present. The most important

risk factors seem to be the presence of pre-existing kidney insufficiency, diabetes mellitus and the volume of contrast used. The use of non-ionic agents⁴ appears to lower the incidence of CN and this has been confirmed in animal models.⁵

nephrotoxicity and the decision to perform the intervention must take into cognisance the risks for and outcomes of CN.

Prevention or mitigation of renal failure after the administration of a radiographic contrast agent has been notably difficult. Previous studies have attempted to identify methods to reduce the incidence of CN, particularly in high-risk groups. Pretreatment with diuretics such as furosemide,^{10,11} or with drugs thought to prevent vasoconstriction, such as calcium channel blockers, adenosine receptor

Table I. Risk factors for contrast-associated nephropathy

Confirmed	Suspected
Serum creatinine > 150 µmol/l	Hypertension
Diabetic nephropathy	Abnormal liver function
Metformin	Older age
Class III/IV congestive heart failure	Concomitant use of loop diuretics
Multiple myeloma	
Volume and osmolality of contrast media used	
Repeat contrast within 48 hours	
Intracardiac injection	
Nephrotoxic drugs (NSAIDs, chemotherapy, cyclosporin A)	

Pathophysiology

The mechanism by which contrast administration induces kidney injury is uncertain. A combination of the following factors appears to be most feasible:

- Reduced renal blood flow and medullary ischaemia related to an inhibition of prostacyclin production and stimulation of the renin-angiotensin system.⁶
- Direct nephrotoxicity and uric acid precipitation.⁷
- Red blood cell sludging.⁸
- The generation of reactive oxygen species.⁹

Preventive strategies

First and foremost is the ever-important fact that the decision to perform the procedure must be debated continuously. Without contrast there would be no

blockers, dopamine, aminophylline,¹² endothelin antagonists,¹³ and atrial natriuretic peptide, have not provided clear benefit and may even be harmful.

Volume expansion with intravenous 0.45% or 0.9% saline (2 - 3 litres prior to the procedure and continued after) has been found to be safe and effective but has not eliminated the condition.

The use of low osmolar, non-ionic contrast agents in patients with mild renal insufficiency has been shown to moderately reduce the risk of CN. In a randomised trial involving more than 1 100 patients, Rudnick *et al.*¹⁴ demonstrated acute nephrotoxicity in 7% of patients receiving the ionic agent diatrizoic acid and in 3% using the non-ionic agent iohexol (p < 0.002). Such data have been confirmed in other studies and the effect is especially noticeable in those with kidney insufficiency and those with diabetes.

N-Acetylcysteine (ACC 200, Salmucol, Parvolex) a thiol-containing antioxidant, has been used to treat a variety of pulmonary diseases and to treat acute paracetamol poisoning. Recently this agent has been used successfully to amend the toxic effects of experimentally and clinically induced ischaemia-reperfusion injuries in the heart, kidney, lung and liver.¹⁵⁻¹⁷ Oxidants activate a signal-transduction cascade and molecular response that may engage the cell-death pathway and provoke apoptosis. Such pathways seem to be sensitive to the prevailing redox state of the cell and are inhibited by NAC. Studies have shown that NAC inhibits cell death induced by ischaemia-reperfusion injury in the kidney, liver and lung, and promotes pathways that lead to repair and survival whenever cells are under oxidant stress.

In a randomised study, Tepel *et al.*¹⁸ administered NAC at a dose of 1 200 mg/day (in divided doses per os) on the day before and on the day of the procedure in all high-risk patients, especially those with kidney insufficiency. In this study all patients received saline intravenously and low-osmolality, non-ionic agents were administered. The expected decline in renal function in these patients was significantly reduced. These data are supported by data from Kay *et al.*¹⁹ who used a similar dosing schedule and showed a lower serum creatinine and higher creatinine clearance in those pre-treated with NAC.

Haemodialysis does not remove the contrast agent given and may increase the risk of CN. A recent study²⁰ concluded that in patients with moderate to severe kidney insufficiency undergoing coronary interventions, periprocedural haemofiltration given in an ICU setting appeared to prevent deterioration in kidney function related to the administration of a contrast agent.²⁰ This is a plausible modality to use in high-risk patients requiring intervention although it does increase the costs of the overall procedure significantly.

It is important to realise that not every increase in serum creatinine following contrast administration is due to the contrast agent. Atheroembolic disease with a rapid decline in renal function or a more slow and indolent decline needs to be consid-

ered in the differential diagnosis. In those patients requiring dialysis following coronary angiography, atheroembolic emboli may be a fairly common cause of kidney insufficiency.

Clinical recommendations

The algorithm proposed in Fig. 1 suggests a practical approach to CN prevention, realising that patients with pre-existing renal impairment alone or three or more of the risk factors detailed in Table 1 pose a significant risk for CN.

Normal kidney function. In patients with normal serum creatinine adequate hydration is all that is necessary. Although

serum creatinine levels may be normal, diabetics, elderly patients and those with reduced muscle mass may have a normal U&E although their creatinine clearance may be reduced thereby imparting a risk for CN.²¹ A calculated creatinine clearance using the Cockcroft-Gault formula $[(140-\text{Age}) \times \text{ideal body weight (kg)}] / [0.8 \times \text{serum creatinine } (\mu\text{mol/l})]$ would easily identify such patients. Preventive measures as for moderate insufficiency could then be instituted.

Moderate/ severe kidney insufficiency (creatinine 150 $\mu\text{mol/l}$ - 250 $\mu\text{mol/l}$, creatinine clearance < 50 ml/min).

- Intravenous volume administration with saline 0.45% or 0.9% for 12 hours before and 6 hours after the procedure.

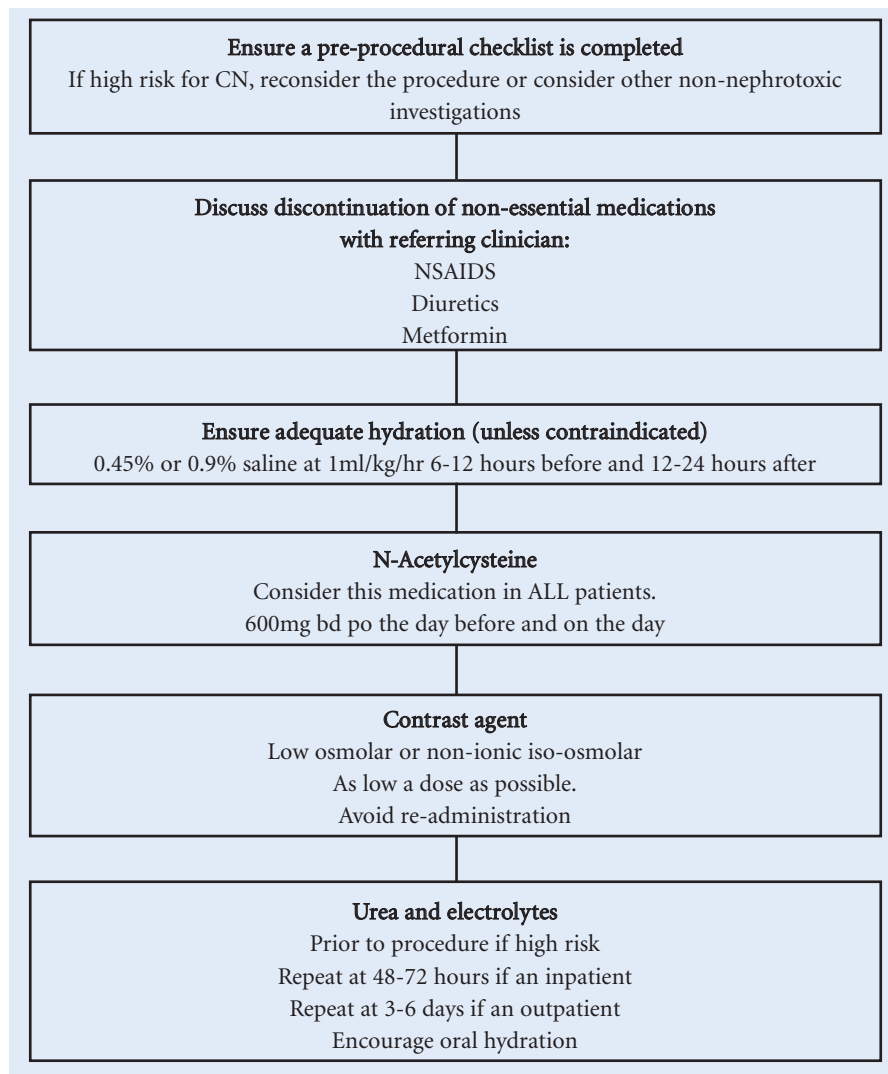


Fig. 1. Recommended peri-procedural methods to prevent contrast nephropathy.

- Low-osmolality, non-ionic contrast agents with judicious dose limitation.
- Acetylcysteine 600 mg twice daily on the day before and on the day of the procedure.

Severe kidney insufficiency (creatinine > 250 $\mu\text{mol/l}$, creatinine < 30 ml/min)

Consider that there is a risk of irreversible kidney failure in such patients despite the abovementioned preventive measures. Such a risk should be discussed with the patient prior to the intervention and the need for the intervention should be debated. In such patients it is imperative to discuss risks with the patient while ensuring adequate hydration; preferably perform the procedure pre-dialysis in those patients receiving chronic dialysis (as dialysis dehydrates patients and may modestly remove contrast), use low-volume iso-osmolar contrast, and monitor renal function closely for 3 - 5 days following transplant.

Practical implications

- Provide generous intravenous hydration, except in the presence of heart failure.
- Avoid postprocedural volume depletion.
- Avoid mannitol and furosemide in patients with kidney insufficiency.
- Minimise contrast volume.
- Allow a 5-day interval between 2 procedures requiring contrast.
- Minimise the development of hypotension and hypoxia.
- Eliminate the administration of other nephrotoxic drugs, e.g. non-steroidal anti-inflammatory drugs (NSAIDs).

Conclusion

Successful prediction and prevention of CN would diminish the morbidity and mortality associated with acute kidney failure related to the administration of contrast agents. Patient convenience and medical care costs would also be optimised by negating the need for prolonged admission, long-term monitoring of kidney function, and the possibility of end-stage kidney failure.

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