Guidelines to prevent contrast-induced nephropathy in patients with acute kidney injury/chronic kidney disease

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A. RECOMMENDATIONS

Most evidence refers to contrast administration in the setting of intra-arterial angiographic procedures where the dose of contrast may be higher than intra-venous procedures such as CT angiography. However clinicians should consider the following recommendations for all contrast procedures in high-risk patients (see flow chart below for definitions).

1. For CT renal angiogram, ICE has a pop-up prompting identification of high-risk patient and will automatically ensure radiology clerk liaise with RDCU. For all other iv contrast investigations you will need to mark radiology request as “FOR ADMISSION TO RDCU FOR IV HYDRATION.. PLEASE RING RDCU EXT. 36332 TO ARRANGE”. The radiology appointment clerks will liaise with Renal Day case Unit (RDCU) regarding a suitable date and will book investigations in the late morning.

2. Intravenous hydration: 0.9 % sodium chloride at 1ml/kg/hr at least for 1 hr prior to procedure and for 4-6 hours after procedure. This regimen was adopted for practical reasons to manage patients in the outpatient setting. For in-patients consider i.v. hydration 12 hours before and after procedure. Avoid i.v. hydration in patients with overt heart failure or if fluid overloaded and in chronic dialysis patients.

3. Consider withholding NSAIDs, ACE inhibitors/ angiotensin receptor antagonists and diuretics for at least 5 days prior to procedure. Caution needs to be exercised whilst withholding diuretics in those with heart failure or if fluid overloaded.

4. N-acetyl cysteine (NAC) is no longer recommended

5. For patients with acute kidney injury requiring haemodialysis, consider timing HD session within 2 hours after contrast administration (except in patients who have intra-arterial procedures e.g. angioplasty, due to risk of bleeding).

6. For all emergency contrast procedures, follow guidelines starting hydration as early as possible but do not delay investigations.
Consider stopping NSAIDs, diuretics**, ACE inhibitor/Angiotensin receptor antagonists 5 days prior to procedure.

Not on dialysis

- eGFR < 30 ml/min/1.73 m²
  - Intravenous hydration***- see text for rate and cautions

- eGFR 30-45 ml/min/1.73 m²
  - Yes
  - Diabetes or multiple myeloma or age > 75
  - No

- eGFR > 45 ml/min/1.73 m²
  - No further intervention

On dialysis

- See text

* Follow guidelines as above for emergency procedure but don’t delay investigations; ** caution in patients with heart failure; *** avoid in patients with heart failure and if fluid overloaded;
B. APPENDIX

1. Rationale

Introduction
The definition of contrast-induced nephropathy (CIN) varies in the literature but a commonly used one is a rise in serum creatinine by 25% from baseline or rise of 44 µmol/L at 48 hours after contrast administration. The incidence of CIN varies from being negligible in those with normal renal function\(^1, 2\) to 4-11% amongst those with mild to moderate renal insufficiency (serum creatinine < 350 µmol/L)\(^3, 4\) and 50% in those with severe renal dysfunction (>350 µmol/L) especially those with diabetes\(^5, 6\).

The development of CIN is associated with increased length of hospitalization and need for dialysis (<1 %)\(^7, 8\). CIN is also associated with in-hospital and long term mortality although a causal relationship is yet to be proven\(^9\).

Risk scores have been developed to identify patients at risk of CIN\(^10, 11\). Risk factors associated with CIN are:

- renal insufficiency (usually creatinine > 130µmol/L or creatinine clearance < 60 ml/min; increasing risk with increasing renal impairment)
- diabetes mellitus with renal insufficiency
- age >75 years
- multiple myeloma
- congestive heart failure
- intravascular fluid depletion
- higher dose and higher osmolality of contrast agent
- hypertension or hypotension
- concomitant anaemia
- concomitant use of NSAIDs

The mechanism by which CIN occurs is not well understood. Possible suggestions are renal vasoconstriction causing ischaemic damage as well as direct nephrotoxicity from contrast. Tubular injury results in the generation of oxygen free radicals. This process is exacerbated by a fall in renal perfusion.

Preventive Strategies:

1. Volume expansion:
Volume expansion may inhibit renin-angiotensin axis, increase vasodilatory renal prostaglandins and decrease medullary hypoxia.
Nearly all the studies were performed in the setting of intra-arterial angiography. Therefore the applicability of these findings to non intra-arterial contrast procedures is questionable. Furthermore the safety of these interventions in patients with heart failure is not known.

**Oral versus intravenous:**
Intravenous hydration may be superior to oral hydration with water alone even in patients with mild renal insufficiency (mean serum creatinine ~ 150µmol/L)\(^{12}\). Oral salt loading with sodium chloride for 48 hours may be equally effective to intravenous saline but these studies were underpowered to detect differences\(^{13, 14}\). There are no studies looking at stopping diuretics for patients already on them. But administration of diuretics increases the risk of CIN\(^{15}\). However as volume expansion is beneficial, withholding diuretics may be a reasonable approach.

**Intravenous fluid type**
Isotonic (0.9%) saline may be superior to hypotonic (0.45 %) saline\(^{16}\). Some studies suggested that isotonic sodium bicarbonate (1.4%) may be equally effective or superior to isotonic saline\(^{17-19}\). A recent systematic review suggested that sodium bicarbonate did not confer additional advantage compared to isotonic saline\(^{20}\). Mannitol or dopamine give no added benefits.

**Fluid regimen**
Most studies have used a rate of 1 ml/kg/ hr for 12 hours prior to and 12 h after procedure. Some studies have used shorter regimens starting 1 hour prior to the procedure and continued for 6 hours after it.

2. **N-acetyl cysteine (NAC):**
NAC is a free radical scavenger and increases production of nitric oxide which counters the vasoconstrictive effects of contrast media. It also increases glutathione concentration which has cytoprotective effects.

**NAC plus hydration versus hydration alone**
The recent and largest randomised (concealed) controlled trial\(^{21}\) including 2308 patients undergoing intravascular angiographic procedure comparing acetylcysteine versus placebo in addition to intravenous hydration in patients at risk of developing CIN showed no benefit. The relative risk for acetyl cysteine was 1.00, 95 %CI (0.81, 1.25) in the entire study cohort. Pre-specified subgroup analyses in those with heart failure, age> 70 years, diabetes, serum creatinine > 132 umol/L did not show any benefit for NAC. The only caveat was that the proportion of patients with eGFR < 30 ml/min/1.73 m\(^2\) in the study was < 5 % and could therefore have potentially lacked power to detect differences in outcome in this high risk group. However, given the lack of overall benefit and in other subgroups, it is reasonable to assume that NAC has no beneficial effect in preventing CIN even in those with
severe renal impairment. The authors of this trial also present an updated meta-analysis of all previous trials to show that the concealment of allocation was inadequate or unclear in the previous trials that had shown benefit favouring NAC. This could have resulted in overestimation of the beneficial effects of NAC in the previous trials.

3. Hemofiltration (HF) and haemodialysis (HD):
Their role is not well established. A single trial including patients with serum creatinine > 176µmol/L showed that short term and 1 year mortality and the need for subsequent dialysis was less in the HF group compared to hydration.

However, a meta analysis of 8 trials comparing HD versus hydration showed no benefit. A more recent trial including patients with serum creatinine > 300 µmol/L showed that compared to hydration HD for 4 hours post-contrast decreased the need for subsequent dialysis (2 % vs 35%, p < 0.001) and the need for permanent dialysis (0 % vs 13 %, p = 0.02).

2. Cost Implications and impact on day case unit workload:
The cost of 1 litre of 0.9% NaCl is £0.46. Over a 3 month period (July-Sept 2011), there were 7 patients under care of the renal unit undergoing contrast related procedures who needed i.v. hydration.

It is difficult to estimate the number of patients needing intravenous hydration during contrast procedures across the entire trust. Furthermore due to logistic reasons of arranging intravenous hydration for outpatients not known to the renal unit, these guidelines will be limited to patients under the care of the renal unit. However, these guidelines could be adopted by other departments for managing in-patients undergoing contrast procedures.

References:


21. ACT investigators. Acetylcysteine for Prevention of Renal Outcomes in Patients Undergoing Coronary and Peripheral Vascular Angiography: Main Results From the Randomized Acetylcysteine for Contrast-Induced Nephropathy Trial (ACT). Circulation 2011;124:1250-59


