Radiocontrast media-induced nephrotoxicity in patients with renal failure: rationale for a new double-blind, prospective, randomized trial testing calcium channel antagonists

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Risk factors for radiocontrast nephropathy

Humans as well as experimental animals with normal renal function do not usually exhibit acute renal failure following radiocontrast media injection. Experimental radiocontrast-induced renal failure requires various preceding stresses, including subtotal nephrectomy, dehydration, congestive heart failure, inhibition of nitric oxide, or prostaglandin synthesis. The major risk factors for radiocontrast nephropathy in humans are: high doses of contrast media, pre-existing renal failure especially in diabetes mellitus patients, dehydration or decreased effective arterial volume (congestive heart failure, cirrhosis, and nephrotic syndrome), as well as other factors favouring pre-renal failure including angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs [1]; multiple myeloma may not be an independent risk factor [2].

Prevention of radiocontrast nephropathy: the classical paradigm

The most simple and 100% effective measure to avoid renal failure is to contraindicate contrast media injection in high-risk patients, and whenever possible to perform magnetic resonance angiography or alternative techniques. The dose of radiocontrast media should be kept to a minimum; for example, selective coronary injections can be performed without aortography. Non-ionic, low-osmolality media should be considered at least in patients with a serum creatinine > 1.6 mg/dl [3].

Although there are no adequate randomized controlled studies to assert the beneficial effect of hydration, it would seem unethical to induce pre-renal failure by limiting fluid intake. Adequate hydration before contrast media infusion may be enough to guard against acute renal failure in patients with moderate renal failure [4,5]. Oral hydration may actually be sufficient [6].

Diuretic regimens have been associated with either no significant benefit (furosemide with crystalloid, mannitol, and low-dose dopamine) [7], or an adverse effect (furosemide or mannitol alone) [5]. Renal failure was observed, even though patients gained weight, excluding secondary pre-renal failure [5].

Various extra-corporeal treatments, immediately after the procedure, have been administered in an attempt to remove radiocontrast media. The clearance of the contrast media is higher with high-flux haemodialysis or haemodiafiltration than with low-flux haemodialysis or haemofiltration [8]. However, extra-corporeal removal of contrast media does not decrease the incidence of acute renal failure in high-risk patients [9,10], suggesting that early damage has already triggered a cascade of pathogenic events, which cannot be reversed.

Better prevention of radiocontrast nephropathy: from pathogenesis to treatment

The rationale for a better prevention of radiocontrast nephropathy is built on pathogenesis. Contrast media injection in experimental animals leads to a short transient increase, followed by a sustained decrease in renal blood flow, increased renal vascular resistance, increased endothelin and adenosine release, and decreased prostacyclin and nitric oxide synthesis [11]. Atrial natriuretic peptide (ANP) is increased, but not enough to prevent the constriction of afferent arterioles. Tubular hypoxia arises particularly in the
medullary region [12], and cytotoxic reactive oxygen species are generated [13].

The first strategy to offset the increase of renal vascular resistance was the use of dopamine. A few studies reported a beneficial effect [14,15], especially in patients with the highest serum creatinine levels [16]. However, most studies were inconclusive [17,18], or even reported a negative effect in patients with peripheral vascular disease [19]. Adrenergic blockade was also ineffective in an experimental model [20].

More specific vasodilator treatments have been tested. Increased endothelin levels were confirmed in humans injected with radiocontrast media, with a compensatory increase in ANP levels [21]. However, endothelin receptor antagonism with an ETA/ETB blocker exacerbated radiocontrast nephropathy [22], and ANP administration had no effect [23].

Adenosine A1 receptor antagonists exhibited some beneficial effects in experimental radiocontrast nephropathies [24–26]. An early clinical study claimed that theophylline, a non-specific adenosine receptor antagonist, prevented the small fall in glomerular filtration rate and effective renal plasma flow seen in the placebo-treated group [27]. However, two recent large trials using theophylline were negative [4,17].

Prostaglandin E1 was used in a randomized study and had a marginally beneficial effect [28], with only borderline significance after statistical adjustment [29].

Decreased nitric oxide formation has been confirmed in humans injected with radiocontrast media [30]. L-Arginine administration aiming at increasing nitric oxide levels was effective in an experimental model [31]; however, intra-arterial delivery before and after the procedure may be difficult in clinical practice.

A recent study in 83 patients supports the use of antioxidant therapy for the prevention of radiocontrast nephropathy [32]. However, serum creatinine levels were not significantly increased in the placebo-treated controls. The difference between groups was only due to a surprising decrease of serum creatinine levels in the acetylcysteine-treated patients [32]. Therefore, additional studies in high-risk patients are required to confirm this observation.

**Calcium channel antagonists for the prevention of radiocontrast nephropathy**

Calcium channel antagonists are capable of reversing the acute haemodynamic alterations induced by radiocontrast administration both in experimental animals [33] and in humans [34]. Calcium channel blockers can prevent the vasoconstriction induced by adenosine injection in experimental animals [35]. Calcium channel antagonists also inhibit the increase of intracellular calcium in isolated rat tubules [36] or rabbit tubular cells [37] exposed to transient anoxia, which could favour subsequent apoptosis [38,39]. Calcium channel antagonists may also inhibit the decrease of nitric oxide synthesis following contrast media administration in humans [30]. However, acute administration of calcium channel blockers before the procedure is not enough to prevent radiocontrast nephropathy [40]. Only one randomized controlled study supports a beneficial effect of calcium channel blockers for the prevention of radiocontrast nephropathy [41]. In that study, patients in the control group did exhibit some decline in renal function. No such decline was observed in the nitrendipine-treated group. However, only 35 patients were included [41].

An ongoing multicentre, international, randomized, double-blind, placebo-controlled trial will test the effect of the calcium channel antagonist amldipine, started 7 days before and continued 2 days after the injection of non-ionic radiocontrast media. Chronic renal failure patients (calculated creatinine clearance between 10 and 60 ml/min) with scheduled intravascular radiographic investigation will be included. They will receive standard hydration with 0.45% saline infusion. The expected reduction in mean calculated creatinine clearance is by 20% in controls, but by only 10% in amldipine-treated patients. To detect such a difference at a significance level of 5% in a two-tailed test with 80% power, 130 patients must be included in each arm. The total number of patients to enter the study will be 290. Results are expected for 2004.

**References**


