

Contrast-Induced Nephropathy: The Wheel Has Turned 360 Degrees

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Contrast-induced nephropathy (CIN) has been a hot topic during the last 5 years due its association with increased morbidity and mortality. CIN is an important complication, particularly in patients with advanced chronic kidney disease (CKD) associated with diabetes mellitus. Methods to diminish the incidence of CIN have been highly contentious. They include choice of contrast, pharmacologic manipulation, and volume expansion. The pathophysiology of this complication remains uncertain, but reduction in renal blood flow and direct toxicity of tubular cells has been implicated. More than 900 publications under the heading CIN have been published during the last 5 years. Fewer than 5% of these publications are randomized prospective controlled studies. In spite of the large number of reports on CIN, very little has been changed. The use of the smallest possible dose of low- or iso-osmolar contrast media, volume expansion, stopping nephrotoxic drugs, and avoiding repeat contrast injections within 48 hours remain the most effective approach to reduce the risk of CIN.

Key words: Contrast media; contrast-induced nephropathy; prevention; pharmacologic manipulation; volume expansion

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Interest in contrast-induced nephropathy (CIN) has been rekindled among nephrologists, radiologists, and cardiologists since 2003 thanks in part to a paper (the NEPHRIC study) suggesting less CIN with use of an iso-osmolar nonionic dimer (1). However, the pathophysiologic explanation for why a nonionic dimer should be less nephrotoxic compared with some of the nonionic monomers is still lacking. In addition, recent studies have not been able to confirm the results of the NEPHRIC study (2–6).

A major issue is that CIN is a diagnosis of exclusion. Usually, when a rapid, and often temporary, reduction in glomerular filtration rate (GFR) is noted, the contrast agent is blamed (7, 8). Despite more than 30 years of research, partly due to the lack of an adequate animal model, the pathophysiology of CIN is still poorly elucidated. Useful animal models of CIN are not available. The continuing importance of CIN is partly due to its association with increased morbidity and mortality

within the 2 years following diagnosis (9–12). Thus, although the mechanism underlying this association is not clear, CIN cannot for now be dismissed as just a temporary dip in kidney function without long-term consequences. The purpose of this paper is to provide a current state-of-the-art review of the field.

Search strategy

We searched the Cochrane Library (2000–2006), PUBMED (2001–01.04.2007), and EMBASE (2001–2006), limited to the languages English, French, German, Spanish, and Danish. The search term was “Contrast Induced Nephropathy.” The search was performed by Povl Jørgensen, Librarian at the academic library of Copenhagen University Hospital Herlev. The search resulted in more than 900 references. Based on the abstract, it was decided whether the complete paper should be obtained.

Definition

CIN is generally defined as an otherwise unexplained increase in serum creatinine of more than 25%, or 44 $\mu\text{mol/l}$ within 3 days after the intravascular administration of a contrast medium (CM). There has been a shift toward this definition since it was proposed in 1999 by the European Society of Urogenital Radiology (13). In severe cases, the increase normally starts within 24 hours (14). More conservative definitions (e.g., creatinine rise $>88 \mu\text{mol/l}$) have a lower sensitivity.

Clinical features

CIN ranges in severity from an asymptomatic, nonoliguric transient form to oliguric severe acute kidney failure necessitating dialysis. Serum creatinine often peaks within 3 to 4 days after the administration of CM (15–17). Fortunately, most episodes of CIN are self-limited, resolving within 1–2 weeks. Permanent kidney damage seems to be uncommon. Milder CIN may be under-recognized in clinical practice because serum creatinine is not routinely measured after CM, especially in outpatients having intravenous CM.

Incidence

The reported incidence of CIN varies among studies, due to differences in definition, background risk, type and dose of CM, imaging procedure, and the frequency of other potential causes of acute kidney failure (18–20). The level of preexisting kidney function is a major determinant of the risk for CIN. The incidence of CIN in the general population is below 2% (21–23). For patients with mild-to-moderate underlying kidney disease, the incidence of CIN is approximately 5 to 10%. Concomitant diabetes mellitus with mild-to-moderate kidney disease increases the risk to 10 to 40%, whereas the incidence of CIN increases to 50% or more in patients with advanced kidney disease (24–26). The incidence of CIN varied from 3% to 45% in the control arms of prospective trials of acetylcysteine (26–29). Despite increased awareness, CIN remains the third most common cause of hospital-acquired kidney failure, being responsible for 11% of cases in 2002 and 12% in 1979 (9, 10). The mortality rate in CIN cases was 14%.

Patients at risk

The highest risk for CIN is seen in those with preexisting kidney disease (serum creatinine $>132 \mu\text{mol/l}$ [1.5 mg/dl]), particularly when due to diabetic nephropathy (1, 8, 13, 30). Diabetes mellitus without renal impairment is not a risk factor (8, 30). The level of kidney function prior to CM administration largely determines the severity of CIN. The occurrence of CIN in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention is associated with a markedly increased mortality as well as with bleeding and restenosis (11, 12, 14, 16). It is not clear to what extent these associations are due to CIN, to preexisting illness severity, or to alternate mechanisms of kidney injury such as atheroembolism (31).

Large doses of CM and multiple injections within 72 hours increase the risk for CIN. The route of administration is also important, and CM seem less nephrotoxic when administered intravenously than when given intraarterially into the renal arteries or the aorta proximal to the origin of the renal blood vessels (32). The acute kidney concentration of CM is much higher after intraarterial than after intravenous administration, and intraarterial injections tend to be repeated during a procedure.

Dehydration and congestive cardiac failure, by causing a reduction in kidney perfusion, enhance ischemia due to CM. The concurrent use of nephrotoxic drugs such as nonsteroidal antiinflammatory drugs (NSAIDs) and aminoglycosides may also potentiate the nephrotoxic effects of CM (13). Kidney dysfunction is found more frequently in patients with hypertension, hyperuricemia, or proteinuria than in patients without these conditions (33). Although multiple myeloma has been considered a risk factor for CIN, this is generally not so if dehydration is avoided (34).

Reducing the risk

It is of utmost importance to identify patients at risk prior to CM administration by identifying those with decreased kidney function (35). GFR below 60 ml/min is a risk factor for CIN. It is not necessary to measure serum creatinine in every patient, but this should be done prior to intraarterial contrast and in patients with a history of kidney disease, proteinuria, kidney surgery, diabetes, hypertension, or gout (33, 35–38). Serum creatinine is

insensitive to early-stage kidney disease, but is an adequate marker for severely reduced kidney function (CKD stages 4 and 5) in those at greatest risk of developing CIN. Given that creatinine production depends on muscle mass, estimates of creatinine clearance, or GFR derived from serum creatinine, use of either the Cockcroft-Gault (39) or Modification of Diet in Renal Disease (MDRD) (40) equations should be employed, despite the inaccuracies of the estimates (41–43). More precise direct measurements of GFR with, for example, radioisotopes or inulin are impractical. Perhaps in the future, cystatin C will provide us with adequate information about kidney function (44, 45).

Choice of contrast media

Through a meta-analysis of comparative trials, Barrett and Carlisle (46) showed the incidence of CIN in patients at risk to be significantly higher after the administration of high-osmolar (HO) CM (osmolality >1500 mOsm/kg) than after low-osmolar (LO) CM (osmolality <915 mOsm/kg). This analysis was confirmed in the largest single trial by Rudnick et al. (30), which clearly demonstrated that patients with preexisting kidney disease alone or with diabetes mellitus had a lower risk of CIN when LOCM was used. Today, HO-CM should be avoided in patients at increased risk of CIN.

The question remains as to whether the other available CM, either LOCM or iso-osmolar CM (IOCM; osmolality 290 mOsm/kg), differ in terms of nephrotoxicity. A total of eight nonionic monomers (iohexol, iomeprol, iopamidol, iopentol, ioxilan, iopromide, ioversol, iobiditrol), one ionic dimer (ioxaglate), and one nonionic dimer (iodixanol) are approved for intravascular use (their use varies from country to country). One nonionic dimer is not approved for intravascular use (iotrolan), and one is under clinical testing (iosimanol).

It is debatable whether all LOCM are equally nephrotoxic. Comparisons across studies suggest differences in nephrotoxic potential between the various monomers (26, 28), but no head-to-head comparisons of nonionic monomers in at-risk patients are available.

Several studies have compared LOCM with IOCM. Some have compared LOCM and IOCM given intraarterially, fewer following their intravenous injection. In 2003, the results of a randomized trial by Aspelin et al. (1) in 129 patients with moderate chronic kidney disease and diabetes mellitus showed a significantly higher incidence of CIN, defined as an absolute increase in serum

creatinine greater than 44 $\mu\text{mol/l}$ (0.5 mg/dl), within 72 hours with intraarterial iohexol than iodixanol (26% vs. 4%). The two groups differed significantly with regard to interventional procedures and duration of diabetes, but were otherwise comparable. Using the same endpoint, Jo et al. (47) did not find a significant difference overall between the IOCM iodixanol and the LOCM ionic dimer ioxaglate in 275 patients with chronic kidney disease undergoing coronary procedures; however, in some subgroups, e.g., patients with diabetic nephropathy, there was a significant difference. The other angiographic studies have not shown any significant difference (Table 1). In a retrospective study of 225 patients with moderate to severe kidney disease, Briguori et al. (49) could not find differences in CIN rates between iodixanol and the LOCM nonionic monomer iobitridol. Neither did Solomon et al. (2) find a difference between iopamidol and iodixanol in a prospective randomized study of 414 patients with kidney disease.

Controversy may exist about differences in nephrotoxicity between IOCM and LOCM following their intraarterial administration, but it is clear there is no advantage of using the nonionic dimer for intravenous studies (Table 2). Recently, Thomsen et al. (4) reported 7% CIN after intravenous injection of 40 g I iodixanol and 0% CIN after iomeron in patients with reduced kidney function ($P < 0.05$). Using the same endpoint as in the NEPHRIC study (1), Barrett et al. (31) showed a 2.6% CIN rate after intravenous injection of iodixanol for computed tomography (CT) and 0% after injection of iopamidol in a randomized, multicenter trial (IMPACT). The results of the IMPACT study were similar to previous, smaller studies by Carraro et al. (50) and Kolehmainen et al. (51) in patients with chronic kidney disease, in which no difference was found between iodixanol and their respective comparators (iopromide and iobiditrol, both nonionic LOCM) (Table 2). No other randomized prospective studies of CIN after intravenous injections have yet been performed.

The only differences in nephrotoxicity between iodixanol and nonionic monomers have been found between the dimer and iohexol, to the advantage of the dimer but only after intraarterial injection. That led Bettmann (26), Sharma and Kini (27), and Solomon and DuMouchel (2) to speculate that there may be a difference in nephrotoxic potential between the various nonionic monomers and iohexol. Solomon and DuMouchel (2) conducted a systematic analysis of published papers and FDA reports of adverse events, and found that the risk of

Table 1. Prospective randomized trials comparing intraarterial iso- with low-osmolality contrast media.

Low-osmolality CM	n	Iso-osmolality CM	n	Examination	Scr	DM	Statistical result	Reference
Iohexol	48	Iodixanol	54	Coronary	3.1	35%	No difference	48
Iohexol	65	Iodixanol	64	Arteriography	1.5	100%	Iodixanol superior	1
Ioxaglate	135	Iodixanol	140	Coronary	1.34	48%	Iodixanol may be superior in certain subgroups	47
Iopamidol	204	Iodixanol	210	Coronary	1.45	41%	No difference	2
Iopamidol	48	Iodixanol	54	Coronary	<2	100%	No difference	5

Scr: serum creatinine; DM: diabetes mellitus.

CIN was higher in patients following iohexol than following another nonionic monomer, iopamidol. Bettmann (26) and Sharma and Kini (27) analyzed control arms of studies of patients with chronic kidney disease receiving no premedication and showed that the average incidence of CIN after iopamidol was significantly lower than after iohexol, whereas the incidence after iodixanol varied from 3% to 33%. Thus, it cannot be excluded that there may be a difference in nephrotoxic potential between the various LOCM. Although there are no important differences in the physicochemical properties of the different nonionic monomeric LOCM, it can be argued that it is inappropriate to put all nonionic monomers in one basket in any review or meta-analysis.

Hydration (volume expansion)

Volume expansion is generally accepted as a means to reduce the risk of CIN, although few studies address this theme directly. Early studies of CIN often described those affected as dehydrated. Intravascular volume expansion may increase kidney blood flow, reduce vasoconstriction in the kidney, reduce the dwell time of contrast within the kidney, improve tubular clearance of uric acid and cast material, and exert variable neurohormonal effects that reduce the rate of CIN. In addition, diuresis associated with effective hydration is associated with an increase in intrarenal production of pro-

stacyclin, leading to vasodilatation in the vulnerable region of the renal medulla.

During the last 15 years, only a few randomized trials examining prophylactic fluid therapy have been published (Table 3). They include patients with normal and decreased kidney function. The fluid has been administered orally, intraarterially, and intravenously. Study sample size has varied from 18 to 1620, but no more than 2500 patients (in total) have participated in these trials. It is clear that forced diuresis by adding mannitol or furosemide to hypotonic saline does not work (57, 62, 63). The same applies to a rapid bolus of isotonic saline (250–300 ml) at the time of CM exposure (52, 56). Unrestricted access to water for 12 hours prior to CM administration is also on the “doesn’t work” list (55). On the “potentially effective” list one finds: 1) hypotonic (0.45%) saline starting 12 hours before and continuing for 12 hours after CM exposure at 1 ml/kg/hour (62); 2) isotonic saline 4 hours before and continuing for 12 hours after CM exposure at 1 ml/kg/hour (53); 3) oral hydration (1000 ml over 10 hours) followed by hypotonic saline (300 ml/hour) starting 0.5 hours before and continuing for 6 hours total (54).

In an initial trial, Merten et al. (58) showed that isotonic bicarbonate starting 1 hour before (3 ml/kg/hour) and continuing for 6 hours after CM exposure (1 ml/kg/hour) reduced the incidence of CIN when compared to isotonic saline given for the same period. There were some methodological weaknesses to this trial. However, Briguori et al.

Table 2. Prospective randomized trials comparing intravenous iso- with low-osmolality contrast media.

Study	Nonionic low-osmolar contrast media	Iodixanol	Criteria
CARRARO et al. (50)	0/32 (iopromide)	1/32	50% ↑Scr
KOLEHMAINEN and SOIVA (51)	4/25 (Iobiditrol)	4/25	44 μmol/l↑Scr
ACTIVE (4)	0/76* (Iomeron)	5/72	44 μmol/l↑Scr
IMPACT (7)	0/77 (iopamidol)	2/76	44 μmol/l↑Scr
Total	4/210 (2%)	12/209 (6%)	

Scr: serum creatinine. * $P < 0.05$.

Table 3. Studies of prophylactic fluid therapy for prevention of contrast-induced nephropathy.

Study	Osmolality/route of contrast	Intervention regimen	Control regimen	Number of participants	Mean baseline kidney function	Outcome measure	Results of intervention vs. control <i>n</i> (%) or mean	Statistical significance
BADER et al. (52)	LOCM/IV	300 ml IV fluid during + 1.5–2.0 l fluid PO (12 hours post)	2 l IV fluid (12 hours pre, 12 hours post)	39	GFR 110 ml/min	Mean change in GFR by contrast clearance at 48 hours	–34.6 vs. –18.3 ml/min/1.73 m ²	<i>P</i> <0.05
MUELLER et al. (53)	LOCM/IA	1 ml/kg/hour IV 0.9% saline (24 hours from morning of procedure)	1 ml/kg/hour IV 0.45% saline (24 hours from morning of procedure)	1383	CrCl 84 ml/min/50 kg lean mass	SCr increase by ≥0.5 mg/dl within 48 hours	5 (0.7%) vs. 14 (2%)	<i>P</i> =0.04
TAYLOR et al. (54)	Multiple/IA	75 ml/hour IV 0.45% saline (12 hours pre, 12 hours post)	1 l water PO (over 10 hours pre), 300 ml/hour IV 0.45% saline (6 hours from call to lab)	36	CrCl 48 ml/min	Mean maximal change in SCr within 48 hours	0.21 v. 0.12 mg/dl	NS
TRIVEDI et al. (55)	LOCM/IA	1 ml/kg/hours IV 0.9% saline (24 hours)	Unrestricted oral fluids	53	CrCl 79.6 ml/min	SCr increase by ≥0.5 mg/dl within 48 hours	1 (3.7%) vs. 9 (34.6%)	<i>P</i> =0.005
KRASUSKI et al. (56)	?/IA	1 ml/kg/hour 0.45% saline (12 hours pre and post)	250 ml 0.9% saline (pre) and 1 ml/kg 0.45% saline (12 hours post)	63	CrCl ≈45 ml/min	SCr increase by ≥0.5 mg/dl within 48 hours	0 (0%) vs. 4 (10.8%)	NS
DUSSOL et al. (57)	LOCM/IA or IV	15 ml/kg 0.9% saline (6 hours pre)	1 g/10 kg weight salt and unrestricted water PO (2 days pre)	153	eGFR 34 ml/min/1.73 m ²	SCr increase by ≥0.5 mg/dl within 48 hours	5 (6.6%) vs. 4 (5.2%)	NS
MERTEN et al. (58)	LOCM/multiple	3 ml/kg/hour (1 hour pre), 1 ml/kg/hour (6 hours post) IV sodium bicarbonate 154 mmol/l	3 ml/kg/hour (1 hour pre), 1 ml/kg/hour (6 hours post) IV 0.9% saline	119	GFR 41–45 ml/min/1.73 m ²	SCr increase by ≥25% within 48 hours	1 (1.7%) vs. 8 (13.6%)	<i>P</i> =0.02
BRIGUORI et al. (59)	IOCM/IA	3 ml/kg/hour (1 hour pre), 1 ml/kg/hour (6 hours post) IV sodium bicarbonate 154 mmol/l plus NAC	1 ml/kg/hour 0.9% saline, (12 hours pre, 12 hours post) plus NAC	220	eGFR 32–35 ml/min/1.73 m ²	SCr increase by ≥25% at 48 hours	2 (1.9%) vs. 11 (9.9%)	<i>P</i> =0.01
RECIO-MAYORAL et al. (60)	LOCM/IA	5 ml/kg/hour IV (1 hour pre), sodium bicarbonate 154 mmol/l plus 2400 mg NAC, unspecified fluid at 1.5 ml/kg/hour (12 hours post), plus NAC 600 mg PO q12h x 2 next day	1 ml/kg/hour 0.9% saline IV (12 hours post) plus NAC 600 mg PO q12h x 2 next day	111	eGFR 75 ml/min/1.73 m ²	SCr increase by ≥0.5 mg/dl within 3 days	1 (1.8%) vs. 12 (21.8%)	<i>P</i> =0.0009
CLAVIJO et al. (61) (not an RCT)	HOCM or LOCM/IA	1 l bolus 5% dextrose in water IA before procedure	Not specified	976	CrCl 44 ml/min	SCr increase by ≥0.5 mg/dl between 24 and 72 hours post	2 (1.4%) vs. 47 (5.7%)	<i>P</i> =0.03

RCT: randomized controlled trial; HOCM: high-osmolar contrast media; LOCM: low-osmolar contrast media; IOCM: iso-osmolar contrast media; IA: intraarterial; IV: intravenous; SCr: serum creatinine; NS: not significant.

recently reported a further trial in which patients having angiography all received N-acetylcysteine (NAC), with one-third also receiving isotonic bicarbonate as per the Merten et al. protocol compared to one-third each receiving 0.9% saline with or without ascorbic acid (59). The lowest rate of CIN was in the bicarbonate/NAC group, but the design of the trial does not permit an assessment of whether there was an interaction between the effect of these agents. Finally, another recent trial comparing a larger dose of bicarbonate together with NAC to saline plus NAC post-angiography also found a lower rate of CIN in the bicarbonate group (60). The interpretation of this trial is somewhat difficult given the larger amount of fluid prior to CM in the bicarbonate group. In using bicarbonate, severe alkalosis should be avoided by not using excessive duration or doses of bicarbonate (7). The mechanism by which bicarbonate is protective is not fully understood, but it has been suggested that increasing the pH of renal medulla and urine by sodium bicarbonate may reduce the production of free radicals and protect the kidney from oxidant injury that can be associated with CIN (58, 64–66). Prolonged intravenous fluid therapy is difficult to administer for ambulatory procedures.

A novel fast strategy of infusing 1 l of 5% dextrose immediately before catheterization was associated with a lower rate (1.4%) of CIN than in a comparison group (5%) in a retrospective study of high-risk patients; further studies are required to test this approach (61).

In conclusion, extracellular volume expansion seems to be the most effective of all the measures used to prevent CIN. The hydration regime should start before and continue for several hours after CM exposure. Normal saline offers better protection than half-strength saline, while isotonic bicarbonate may be the fluid of choice if recent data are correct. The optimal duration and intensity of fluid therapy remains to be fully established.

Pharmacologic manipulation

In recent years, it has been claimed that various substances or drugs may protect the kidney against CIN. However, no intervention has proven efficacious beyond doubt. Strongly positive initial trials have often not been replicable.

NAC might reduce the nephrotoxicity of contrast through antioxidant and vasodilatory effects (18). The results of an initial trial were dramatic, but the event rate in the controls was unexpectedly high for patients given low-dose intravenous low-osmolality

contrast (20, 67–71). Subsequent trials have largely involved patients with reduced kidney function having cardiac angiography. Some have shown benefit and others not; many are limited by low power and a lack of blinding. The dose of NAC employed in most trials has not been chosen based on pharmacologic principles. Two trials comparing doses of NAC have suggested that higher doses may be required, especially if higher doses of contrast are being employed (69, 70). Several meta-analyses of trials of NAC have been reported (20, 67, 71–77). The trials included in these analyses vary. The results of meta-analyses must be interpreted with caution, given the heterogeneous results of the individual trials, and the possibility of publication bias, with small negative studies under-represented (75–77). Also, the effect of NAC on outcomes other than minor changes in serum creatinine is largely unknown. Indeed, studies in healthy volunteers have suggested that NAC might have an effect on creatinine levels unrelated to an effect on GFR (45, 78). Poletti et al. (79) found no effect of NAC when they used cystatin C as the measure of glomerular filtration rate, but they found a significantly lower CIN rate in the NAC group than in the control group when they used serum creatinine as the measure of renal function. Cystatin C is not secreted by the tubular cells, whereas creatinine is. Considering these observations, there is no conclusive evidence that N-acetylcysteine provides consistent protection against CM-induced nephropathy, and its routine use as a prophylaxis should not be recommended.

Ascorbic acid as an antioxidant has been tested in two randomized trials with patients undergoing cardiac angiography (59, 80). In the first study, CIN occurred in 11 (9%) cases given ascorbic acid versus 23 (20%) given placebo ($P=0.02$) (80). However, these results are difficult to interpret as the baseline serum creatinine level was lower in the placebo group and both groups reached a similar level post-contrast. In the more recent trial, ascorbic acid given with NAC and saline was associated with the same rate of CIN as when NAC and saline alone were given (59).

Theophylline and aminophylline (nonselective adenosine receptor antagonists) have the potential to reduce CIN by antagonizing adenosine-mediated vasoconstriction. These drugs have been tested in several small trials. Recent meta-analyses found that the mean rise in serum creatinine was significantly, but only slightly, lower at 48 hours after contrast among those receiving active therapy compared to placebo (81, 82). The clinical importance of this

finding is not clear (4, 22). There was heterogeneity among studies with regard to changes in serum creatinine. There is potential for adverse effects with theophylline, particularly in patients with ischemic heart disease. The optimal dose for prevention of CIN has not been established. Further studies using selective adenosine receptor (A1) antagonists are warranted.

Several other interventions have been proposed to reduce the risk of CIN, but data are limited to support them. Forced diuresis with furosemide, mannitol, dopamine, or a combination of these given at the time of the contrast exposure has been associated with similar or higher rates of CIN when compared to prophylactic fluids alone (62, 63, 83–85). Negative fluid balance might underlie some of the detrimental effects.

Generally small randomized trials of vasodilatation with dopamine, fenoldopam, ANP, calcium channel blockers, prostaglandin E₁, or a nonselective endothelin receptor antagonist failed to show a reduction in the rate of CIN compared to fluid therapy (84–91).

Two studies of captopril as a prophylactic agent yielded divergent results (92–94). In the first trial, serum creatinine rose by more than 0.5 mg/dl (44 μmol/l) in two (6%) patients given captopril for 3 days versus 10 (29%) given placebo ($P < 0.02$) (92). In the second study, CIN was reported as occurring in five (10%) patients given captopril versus one (3%) given placebo ($P = 0.02$) (93, 94).

Prophylactic extracorporeal therapy

While hemodialysis can effectively remove CM from the circulation, preventive dialysis has not been shown to reduce CIN rates (95–98). Given the usual CM volumes administered, there is no need to schedule the dialysis in relation to the injection of iodinated CM for patients already on dialysis. In a trial of prophylactic hemofiltration in an intensive care unit before and after contrast, involving patients with a mean creatinine clearance of 26 ml/min undergoing cardiac procedures, a 25% increase in serum creatinine was seen in three (5%) cases undergoing hemofiltration versus 28 (50%) cases given fluid alone ($P < 0.001$) (99). These results were replicated in a further trial by the same investigators, in which they also showed that hemofiltration limited to the postcontrast period was not significantly different to saline alone (100). However, as changes in serum creatinine during and soon after hemofiltration are affected by creatinine removal, such changes in serum creatinine do not reliably

reflect changes in kidney function. The mechanism of benefit, if any, to the kidney remains speculative. Marenzi et al. suggest controlled high-volume administration as one possibility (100), but their hemofiltration protocol should lead to a neutral, not positive, fluid balance. In both trials, hemofiltration, especially pre- and post-contrast, was associated with reduced in-hospital cardiovascular mortality, but the mechanism by which this might occur is unclear. Given the resource implications and the problems with interpreting the true effect on kidney function, hemofiltration is not recommended at this time as a means to prevent CIN.

Gadolinium-based contrast media

It has been proposed that gadolinium-based CM be used in place of iodinated media in patients at increased risk of CIN. However, Sam et al. (101) showed in a retrospective analysis that the incidence of CIN (defined as anuria) after intravenous administration of gadolinium-based CM was 1.9%, and after intraarterial administration 9.5%. Dialysis was necessary in 40% of those developing anuria. However, the dose of the gadolinium-based CM was triple that usually employed for magnetic resonance (MR) studies. One patient with diabetic nephropathy developed anuria after 0.14 mmol/kg gadodiamide but not 2 years earlier after 120 ml of 350 mg I/ml iohexol (102). Renal biopsy in a patient who developed acute renal failure after 0.18 mM/kg body weight gadodiamide showed acute tubular necrosis, marked proliferation of tubular cells with mild interstitial edema, and inflammation, but without glomerular and vascular changes (103). However, the risk of acute kidney injury after standard-dose gadolinium-based CM for MRI (0.1 mM/kg body weight) is lower than that following the dose of iodinated medium used for CT and cardiac angiography (e.g., 150 ml of 350 mg I/ml). Another problem is that the patient group at increased risk of CIN with iodine-based CM is also at increased risk for nephrogenic systemic fibrosis (NSF), a late severe adverse reaction linked to some of the gadolinium-based CM (104).

Metformin

The biguanide metformin is used for treatment of non-insulin-dependent diabetes mellitus and polycystic ovarian syndrome. Approximately 90% of metformin is eliminated via the kidneys within 24 hours of a dose, but retention of the drug may

be expected in those with reduced kidney function, and there is potential for resulting fatal lactic acidosis. Metformin should not be used in patients with significant kidney disease (105). While the exact level of GFR below which the drug is unsafe has not been rigorously established, it is likely between 40 and 60 ml/min. The use of CM in patients receiving metformin should be done with care as CIN, if it occurs, may lead to retention of metformin and possibly lactic acidosis. It is recommended that metformin be held in patients about to receive CM (106). Intravascular CM administration has not been associated with metformin-induced lactic acidosis in patients with serum creatinine <130 µmol/l. CIN should be excluded by rechecking serum creatinine before metformin is resumed.

Treatment

The treatment of CIN begins with recognition of the condition. For high-risk patients, measurement of serum creatinine between the 2nd and 4th day post-CM will identify the nonoliguric form of CIN. In the oliguric patient, a 24-hour urine volume <400 ml may suggest the diagnosis. There is no specific treatment for CIN (35). Hemodialysis should be employed if required by the severity of kidney failure (95, 96). The acute management of CIN is similar to that for patients with acute kidney injury due to other causes and should include careful monitoring of serum electrolytes to detect hyperkalemia, meticulous attention to fluid balance to prevent hypo- or hypervolemia, daily serum creatinine measurements, and adequate nutritional intake. Use of mannitol or diuretics to increase urine flow in acute kidney injury does not improve, and may worsen, clinical outcome. Affected patients should not be re-exposed to CM before kidney function has returned to its previous or a new stable level. If contrast is to be given again, the patient must be adequately hydrated (35).

Guidelines

In a review published in 2006, Barrett and Parfrey (31) recommended the use of intravenous saline prophylaxis and the lowest possible dose of low-osmolality contrast media in high-risk patients. Nonsteroidal antiinflammatory drugs and diuretics should be withheld for at least 24 hours before and after exposure to contrast medium. The use of N-acetylcysteine was not recommended routinely, given the inconsistent results of clinical trials

(75–77). These recommendations are in accordance with ESUR guidelines from 1999 (13). In the meantime, the wheel has turned 360 degrees. During those 8 years, several guidelines and reviews had been published with various recommendations mainly based one or two original studies; they have not resulted in a better understanding of CIN, but have caused some confusion and uncertainty (7). An evaluation of the plethora of reviews and guidelines concluded that guidelines should be provided through careful study of the published literature and a deep understanding of the subject, and recommendations should be evidence-based whenever possible, relying on consistent results of well-structured large studies. Recommending a change in clinical practice based only on a single study cannot be justified, particularly in the field of CIN, since the inconsistency of results of clinical studies is a real problem. Clinical investigation of CIN regularly faces the problem of finding a perfect-matching control group, as there are many variables that can influence kidney function. In addition, it is important to emphasize that the meta-analysis of inconsistent study results cannot offer confident recommendations about treatment, as clearly shown by several meta-analyses of N-acetylcysteine studies (75–77). Large, definitive randomized clinical trials are strongly needed. In areas of contention, a consensus amongst experts on the subject could be sought. Guidelines should be concisely and clearly written, using accurate terminology and avoiding vague recommendations. Lengthy guidelines are usually not practical and can be confusing.

Conclusion

The use of CM for imaging is increasing. CM are increasingly being used in older patients, a group with a higher prevalence of reduced kidney function. Patients with CKD stages 3, 4, and 5 are subject to an increased risk of CIN (as well as of NSF (104)). When contrast-enhanced imaging is required, the risks with iodinated media have to be considered against the risks with gadolinium chelates. Despite a huge number of studies and reviews of CIN during the last 5 years, in reality nothing has changed (7). No prophylactic pharmacologic agent has been proven to work consistently (35). Prophylaxis using fluids is recommended, but based on small trials (Table 3). Whenever possible, concomitant nephrotoxic drugs should be stopped. There does not appear to be a difference in nephrotoxic potential between the nonionic dimer and various

nonionic monomers, but more late skin reactions have been reported after the dimer than the monomers (107). The wheel has certainly turned 360 degrees over the last 8 years; we are now back at the start, and our understanding of CIN has not been greatly improved. The recommendations for reducing the risk of CIN thus remain unchanged: 1) use the smallest possible dose of low- or iso-osmolar contrast media, 2) organize volume expansion, 3) stop nephrotoxic drugs, and 4) avoid repeat contrast injections within 48 hours.

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