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EDITORIAL

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How to protect from Contrast Media-induced nephropathy?

Contrast media-induced nephropathy (CIN) is the major drawback of contrast media (CM) in invasive cardiology. CIN represents the third common cause of hospital acquired renal failure. It describes the new onset or exacerbation of renal dysfunction after application of contrast media in the absence of other causes. It is usually defined as an increase of serum creatinine from baseline by more than 25% or absolute more than 0.5 mg/dl. CIN appears 24–48 h post exposure with a creatinine maximum 5–7 days later. Only 1.5% of patients without diabetes and with normal renal function suffer from CIN. It occurs in 7–12% of patients with preexisting renal insufficiency and in about 33–48% of patients with both renal insufficiency and diabetes mellitus [1, 2].

Mechanism of CIN is complex and not fully understood. The kidney is the most irrigated organ per tissue weight. Therefore, it is more exposed to exogenous circulating toxins than many other organs. Tubular mechanisms of ion transport may facilitate drug entry into renal tubular cells. Contrast media show direct cellular interaction, osmolality-dependent or viscosity-dependent hemodynamic effects, finally resulting in medullary hypoxia [3, 4]. Furthermore, CM leads to an increased workload of the kidney. In patients with impaired renal function, the combination of hypoxemia and an increased workload could cause acute renal failure. Different independent predictors of CIN were identified. The risk of CIN is especially increased with dehydration before CM application [4].

The randomized trial published by Reinecke et al. includes 424 consecutive patients with elevated serum creatinine concentrations undergoing elective coronary angiography. All patients received hydration. One group received no additional therapy, patients in the second group underwent hemodialysis, and the third group received oral N-acetylcysteine (ACC). The relative risk for CIN from 48–72 h was not affected with oral ACC [5]. Acetylcysteine is a thiol-containing agent with antioxidant properties. For more than 30 years, it has primarily been used as mucolytic. Free radicals are claimed to play an important role in the development of CIN. To date, several randomized trials have studied the impact of ACC in the prevention of CIN. Initial clinical data [6] indicated a dramatic reduction of CIN by orally administered ACC (Table 1). However, this enthusiasm was tempered by a large number of negative trials including the present work by Reinecke et al. [5] (Table 2). Despite positive results of meta-analyses [7, 8], the number of patients included in negative trials clearly exceeds the number in positive trials (Table 2). Other meta-analyses point to inconsistent trial designs [9–11]. Besides one study in patients undergoing primary angioplasty [12], there is no clear evidence of a reduction of 'hard' endpoints such as death, myocardial infarction, or the need for chronic dialysis treatment by the administration of ACC. A direct effect of ACC on serum creatinine levels and estimated GFR could be demonstrated, whereas cystatin C concentrations are not influenced

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Table 1 Positive trials of acetylcysteine (ACC) in the prevention of contrast media-induced nephropathy (CIN). Risk of CIN in the control group and the group with ACC

Author	Design	n	Control (%)	ACC (%)	p	Rel. risk	Remarks
Tepel, 2000	CT, ACC 600 mg orally twice daily for 2 days	83	21	2	0.001	0.1	chronic renal insufficiency (serum-creatinine 2.4 ± 1.3 mg/dl) CIN: increase of > 0.5 mg/dl after 48 h
Diaz-Sandoval, 2002	CA, ACC 600 mg orally twice a day, one dose before and 3 doses after the procedure	54	45	8	0.005	0.2	CIN: serum crea > 25% above the baseline level 48 h after procedure
Ochoa, 2002	CA, ACC 1000 mg orally 1 h before and 4 h after the procedure	80	25	8	0.051	0.3	Creatinine clearance < 50 ml/min CIN: increase of Cr ≥ 0.5 mg/dl or ≥ 25% 48 h after procedure
Shyu, 2002	CA, ACC 400 mg orally twice daily for 4 doses starting 24 h prior to procedure	121	24.6	3.3	0.001	0.1	Chronic renal insufficiency (mean serum crea 2.8 ± 0.8 mg/dl) CIN: increase of > 0.5 mg/dl after 48 h
Baker, 2003	CA, ACC 150 mg/kg immediately before the procedure, followed by 50 mg/kg for 4 h	80	21	5	0.045	0.3	Patients with stable renal dysfunction CIN: serum creatinine > 25% above the baseline level 48 or 96 h after procedure
Efrati, 2003	CA, ACC 1000 mg orally twice daily for 48 h	49	8	0		0.2	Results at 96 h after procedure
Kay, 2003	CA, ACC 600 mg orally twice a day for 4 doses starting 24 h prior to procedure	200	12	4	0.030	0.3	Patients with stable moderate renal insufficiency (creatinine clearance < 60 ml/min [1.00 ml/s]) CIN: serum creatinine > 25% above the baseline level 48 h after procedure
MacNeill, 2003	CA, ACC 600 mg orally, two doses prior, three times after the procedure	43	32	5	0.046	0.2	Baseline serum creatinine ≥ 1.5 mg/dl CIN: 25% increase in baseline creatinine after 72 h
Miner, 2004	CA, ACC 2–3 × 2000 mg orally	171	22.2	9.6	0.040	0.4	Moderate renal dysfunction CIN: > 25% increase in serum creatinine level 48–72 h after PCI no long-term benefit of ACC
Marenzi, 2006	Primary angioplasty in acute myocardial infarction; ACC 600 mg intravenous bolus and 600 mg orally twice daily for 48 h, or 1200 mg intravenous and 1200 mg orally twice daily for 48 h	354	33	15 8	0.001	0.5 0.2	CIN: 25% increase in baseline creatinine

CT computer tomography, *CA* coronary angiography. Total number of patients: n = 1235

[13]. In conclusion, the current practice of ACC administration in patients with impaired renal function seems questionable.

One trial with high risk ICU patients reported that hemofiltration was effective in the prevention of CIN [14]. In contrast, the findings of earlier trials removing contrast media by hemodialysis [15, 16] are consistent with the results of the study published in this issue of *Clinical Research in Cardiology*. The relative risk for CIN from 48–72 h was increased with hemodialysis treatment by 2.9 fold. The authors conclude that hemodialysis in addition to hydration therapy for the prevention of CIN provides no evidence for any outcome benefit but evidence for probable harm [5]. At this point of time, the use of extracorporeal removal of contrast agent cannot be recommended.

Another important issue represents the choice of the contrast agent. Historic trials comparing ionic high-osmolar with nonionic low-osmolar CM demonstrated a relevant benefit of low-osmolar CM in patients at elevated risk for CIN [17]. The newest CM generation, nonionic dimeric CM are controversial because they are associated with an significantly elevated incidence of late adverse effects [18]. Schering took its nonionic dimer off the market years ago as a precautionary measure. The only substance of this kind now at the market is iodixanol (Visipaque®). A randomized trial in 129 diabetic patients with mild to moderate renal failure reported that iodixanol significantly

Table 2 Negative trials of acetylcysteine (ACC) in the prevention of contrast media-induced nephropathy (CIN). Risk of CIN in the control group and the group with ACC

Author	Design	n	Control (%)	ACC (%)	p	Rel. risk	Remarks
Allaqaband, 2002	CA+PA, ACC 600 mg twice a day for 4 doses starting 24 h prior to procedure (oral) + hydation	85	15.3	17.7	Ns	1.2	Baseline creatinine >1.6 mg/dl CIN: >0.5 mg/dl increase after 48 h
Briguori, 2002	Coronary and peripheral angiography; ACC 600 mg orally twice a day for 4 doses starting 24 h prior to procedure	183	11	6.5	Ns	0.6	Serum creatinine 1.5±0.4 mg/dl CIN: serum crea >25% above the baseline level 48 h after procedure
Durham, 2002	CA, ACC 1200 mg orally 1 h prior and 3 h after the procedure	79	22	26.3	Ns	1.2	Serum creatinine >1.7 mg/dl CIN: increase of 0.5 mg/dl
Kahlon, 2002	CA, ACC 600 mg orally for 4 doses	51	16.7	29.6		1.8	Results at 96 h after procedure
Vallero, 2002	CA, ACC 600 mg orally twice a day for 4 doses starting 24 h prior to procedure	100	0 (7.5)	16.6 (8.5)	Ns	(1.1)	Baseline creatinine >1.2 mg/dl CIN: >0.5 mg/dl increase after 48 h
Boccalandro, 2003	CA, ACC 600 mg orally twice a day for 4 doses starting 24 h prior to procedure	179	12	13	Ns	1.1	Patients with renal insufficiency
El Mahmoud, 2003	CA, ACC 600 mg orally twice daily before and after procedure	120	3.3	5		1.5	CIN: increase of 25% in serum creatinine level after 48 h
Loutrianakis, 2003	CA, ACC 600 mg orally + fenoldopam twice daily before and day of procedure	47	13	25		1.9	After 5–7 days
Oldemeyer, 2003	CA, ACC 1500 mg orally twice a day for 4 doses starting the evening before the procedure	96	6.4	8.2	Ns	1.3	Baseline serum creatinine >1.2 mg/dl CIN: increase of >0.5 mg/dl or an increase of ≥25% in serum creatinine after 48 h
Fung, 2004	CA, ACC 400 mg orally 3 times daily before and day of procedure	91	13.3	17.4	0.8	1.3	Serum creatinine level before: 1.69–4.52 mg/dl CIN: >0.5 mg/dl increase after 48 h
Goldenberg, 2004	CA, ACC 600 mg orally three times a day for 4 doses	80	8	10	Ns	1.3	Serum creatinine level before: 2.0±0.39 mg/dl CIN: >0.5 mg/dl increase after 48 h
Webb, 2004	CA, ACC 500 mg, iv	487	20.7	23.3	0.57	1.1	Negative, terminated early
Azmus, 2005	CA, ACC 600 mg orally twice daily for 5 doses starting day before procedure	397	8.4	7.1	0.64	0.8	CIN: increase of 25% in serum creatinine after 24 h and 48 h
Gomes, 2005	CA, ACC 600 mg orally twice daily before and day of procedure	156	10.1	10.4	1.00	1	CIN: >0.5 mg/dl increase after 48 h
Huber, 2006	Different radioangiographic procedures, ACC 600 mg intravenously twice daily before and day of procedure	91	2	12	0.047	6	Control group treated with theophylline 200 mg CIN: >0.5 mg/dl increase after 48 h
Reinecke, 2007	CA, ACC 600 mg orally twice a day for 4 doses starting 24 h prior to procedure	424	6.1	5.3	Ns	0.9	

CT computer tomography, *CA* coronary angiography. *Ns* non significant. Total number of patients: n=2666

decreased CIN incidence from 26 to 3% compared to the nonionic monomeric iohexol [19]. These findings were confirmed by the RECOVER study [20]. In contrast to these findings, other trials reported a higher incidence of CIN with iodixanol: 20.5% in the RAPPID study [21] and 33.3% in the CONTRAST study (compared with 25.3% of those treated with other contrast agents) [22]. Recent meta-analyses found the incidence of CIN with iodixanol comparable to that with monomeric nonionic contrast agents like iopamidol, iopromide, or iomeprol [11, 23]. Therefore, further controlled and randomized clinical data are necessary to validate the role of iodixanol in the prevention of CIN.

Hydration remains the most important protection against CIN. In the past, hydration with 0.45% saline was the recommended protection [24]. Newer randomized data in patients undergoing coronary angioplasty suggest a further advantage by isotonic hydration [25].

In conclusion, the well conducted study by Reinecke and coauthors shows that hydration alone remains the best preventive measure. Before contrast media application in invasive cardiology, nephrotoxic treatments should be discontinued. The dose of contrast has to be minimized. Low osmolar contrast media should be preferred. There is no general recommendation on dimeric nonionic isoosmolar CM or ACC in the prevention of CIN. Routine hemodialysis after contrast administration seems to be harmful.

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