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REVIEW

Toxicity of contrast media: an update

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ABSTRACT

Renal toxicity of iodinated radiocontrast media (contrast-induced nephropathy; CIN) is a major cause of acute renal failure in hospitalised patients. Magnetic resonance imaging (MRI) is applied as an alternative technique but the use of gadolinium (Gd) containing contrast media carries the risk of nephrogenic systemic fibrosis (NSF), a potentially lethal disorder that occurs especially in patients with renal failure. In this article we give an update of the literature on toxicity of radiocontrast media and on preventive measures.

Risk of nephrotoxicity of iodinated contrast media can be reduced by identification of high-risk patients. In these patients pre- and post-hydration with isotonic saline should be applied. When there is insufficient time to prehydrate, a short infusion protocol with sodium bicarbonate is preferable. There is a lack of evidence to support the use of oral or intravenous N-acetylcysteine or iso-osmolar contrast media. In order to prevent NSF, linear gadolinium chelates should not be used in patients with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min. In patients with eGFR between 10 and 30 ml/min the small chance of NSF with cyclic Gd-containing chelates must be balanced against the high risk of developing CIN, and the morbidity and mortality associated with the start of dialysis. In patients without residual renal function, the small chance of developing NSF after macrocyclic Gd-enhanced MRI imaging may tip the balance to the use of iodine containing contrast media.

KEYWORDS

Contrast, gadolinium, nephropathy

INTRODUCTION

Iodinated radiocontrast media are frequently used in radiological procedures such as computerised tomography (CT) scans, angiography, and interventional cardiology procedures. These media can cause acute renal failure. Acute renal failure induced by radiocontrast media, which is known as contrast-induced nephropathy (CIN), is the third most common cause of new onset renal failure in hospitalised patients.[1] In patients undergoing coronary interventions, the incidence of CIN (defined as a rise in serum creatinine concentration of more than 25%) was 14.5% and the incidence of end-stage renal failure was 1.3%.[2] The development of CIN not only increases length of hospital stay but is also associated with an increased mortality rate.[3] Prevention of renal damage due to radiographic contrast media is one of the ten items in a national campaign to improve safety in Dutch hospitals. The optimal protocol for prevention of CIN has been subject of debate. Recently, the Dutch Institute for Healthcare Improvement, the CBO, has published guidelines for the prevention of CIN.[4] *Table 1* summarises the guideline proposals. From the guidelines it is evident that it is important to identify high-risk patients. The most important determinant of risk is baseline renal function. Patients with renal insufficiency are at highest risk of developing CIN.

Since the conception of the guidelines, results of several new studies on CIN have been published. Moreover, magnetic resonance imaging (MRI) is often advocated as an alternative to avoid CIN in patients with renal insufficiency. However, concern has risen about the toxic side effects of the gadolinium-containing contrast media used in MRI, especially the occurrence of nephrogenic systemic fibrosis (NSF).[5]

In this article we present an update on the toxicity of contrast media and preventive measures.

IODINATED CONTRAST MEDIA-INDUCED NEPHROPATHY

Iso-osmolar contrast media

Iodinated contrast media can be classified into three groups according to their osmolarity: high-osmolar

Table 1. *Summary of CBO guideline on prevention of radiocontrast nephropathy*

Low-risk patient		Withdraw diuretics and NSAID 24 hours before contrast exposure Instruct patients to take sufficient fluid and salt in order to prevent dehydration
High-risk patient	• Waldenstrom/Kahler disease with light-chain proteinuria • eGFR <45 ml/min/1.73 m² • eGFR 45-60 ml/min/1.73 m² with diabetes mellitus or two additional risk factors: peripheral vascular disease, heart failure, age >75 years, anaemia, symptomatic hypotension, high volume of contrast, dehydration, use of diuretics and/or NSAID	Pre- and post-hydration: NaCl 154 mmol/l; total amount 12 to 16 ml /kg before and a similar amount after contrast exposure. Infusion rate may be 250 ml/min, a lower infusion rate and/or a lower volume is indicated in patients with heart failure or severe renal failure (eGFR <20-30 ml/min) In case of emergency procedure: $NaHCO_3$ 154 mmol/l, 1 hour before at a rate of 3 ml/kg/h and for 6 hours after contrast exposure at a rate of 1 ml/kg/h

NSAID = nonsteroidal anti-inflammatory drug; eGFR = estimated glomerular filtration rate.

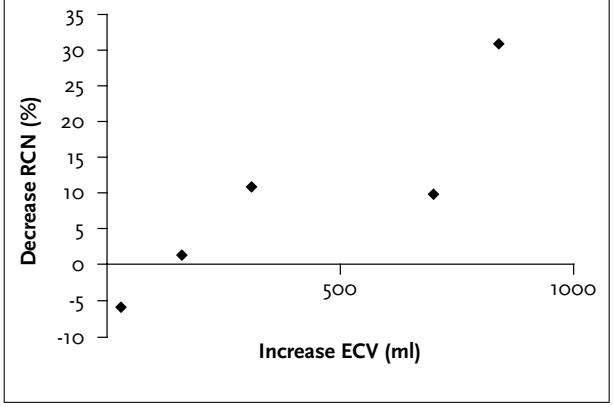
contrast media (HOCM, 2000 mOsm/kg), low-osmolar contrast media (LOCM 600-800 mOsm/kg) and iso-osmolar contrast media (IOCM 290 mOsm/kg). There is clear evidence that LOCM have a lower risk of CIN than the conventional HOCM.[6,7] In order to further reduce side effects, IOCM have been introduced. In a meta-analysis it was concluded that the risk of CIN was indeed lower after IOCM as compared with LOCM (OR 0.39).[8] However, analysis of the three studies that contributed to this result raises doubt on the validity of this conclusion.[9-11] None of these studies used an adequate pre- and post-hydration regimen. The study by Aspelin was performed in diabetics, and the patient groups were not completely matched: in the LOCM group duration of diabetes was five years longer. Also, glomerular filtration rate at baseline was probably lower in the LOCM group, which included a higher percentage of women and patients with a higher body weight. Several studies that were not included in this meta-analysis did not show a benefit of iso-osmolar contrast media.[12-14] The most recent study was published in 2007.[15] This was a randomised controlled trial that included 482 patients who underwent a cardiac angiography with or without an intervention. Subjects were randomised to receive either the low-osmolar agent iopamidol or the iso-osmolar agent iodixanol. All patients received an isotonic bicarbonate solution as preventive strategy (see below). No differences in CIN were noted between both groups. This study thus does not provide evidence of any advantage of IOCM either, although it cannot be excluded that differences between the various LOCM contribute to the divergent results. A pathophysiological explanation for the disappointing results of IOCM might be the impaired renal blood flow caused by an increase in blood viscosity that was demonstrated by *in vitro* animal studies.[16]

In conclusion: there is insufficient evidence that iso-osmolar contrast media are better than low-osmolar contrast media.

Hydration

There is almost unanimous agreement in the literature that appropriate hydration prevents contrast-induced nephropathy. It is therefore rather surprising that there are only a limited number of studies that support this conclusion. Hydration was compared with placebo in one study only.[17] Other studies have compared different hydration regimens consisting of (combinations of) isotonic saline, hypotonic saline or oral water given as bolus or continuous infusion.[18-21] We have analysed these studies and specifically examined the relation between the change in extracellular volume (ECV) and the treatment effect. We calculated the increase in ECV volume for a hypothetical patient, using a ratio of extracellular : intracellular volume of 1:2. Thus, for example, 1000 ml of isotonic saline increases ECV by 1 litre, whereas 1000 ml of water increases ECV by 0.33 litre. The difference in the incidence of CIN was correlated with the change in ECV (*figure 1*). From these data we can conclude that the best regimen is the one that most effectively increases extracellular volume. This can best be

Figure 1. *Relation between the change in extracellular volume (ECV; ml) and the decrease in contrast-induced cephropathy (CIN; %)*



done with isotonic saline, given in the hours before contrast medium infusion. Preferably, ECV should be increased by 500 to 1000 ml. The rate of hydration does not seem important for protection but should be governed by clinical factors that determine the risks of ECV volume expansion, such as heart failure and severe renal insufficiency.

A more practical protocol might be oral supplementation of NaCl instead of intravenous hydration. One study has indeed shown that oral NaCl in a dose of 1 g/10 kg bodyweight per day for 48 hours can be as effective as prehydration with isotonic saline at a rate of 15 ml/kg for six hours.[22] More studies are needed to document the feasibility of this outpatient protocol in routine practice.

N-acetylcysteine (NAc)

The use of N-acetylcysteine (NAc) for the prevention of CIN is heavily debated. The recent CBO guidelines concluded that there was insufficient evidence to support the routine use of NAc. Many have argued against this conclusion. New data were summarised in a recent meta-analysis. This meta-analysis included 30 trials in which NAc was used.[23] Although there was a significant subgroup heterogeneity, the authors concluded that NAc was more renoprotective than hydration. They advised the use of NAc in routine clinical practice, particularly since the oral administration of NAc is safe and extremely inexpensive. However, the data do not support this conclusion. The meta-analysis included 30 randomised controlled trials. Overall, CIN occurred in 229 of the controls and in 147 of the Nac-treated patients. This difference in event rate is fully explained by the results of nine trials. One study is published in abstract form only. The remaining eight trials are summarised in *table 2*.[24-31] It is evident that only two trials used NAc according to the standard protocol of orally administered NAc, 600 mg twice daily on the day before and after the procedure. Two studies used NAc intravenously, three trials administered oral NAc immediately before the procedure, and one study used a lower dose of NAc.

Furthermore, the meta-analysis of Kelly *et al*. did not include four studies that were included in the previous meta-analysis. Still, both meta-analyses used the same criteria for selection of the studies. Three of these studies did not show an advantage of NAc.

The latest meta-analysis adds to the list of the many meta-analyses on the role of NAc in preventing CIN. The conclusions have varied, and interpretation is difficult due to the heterogeneity of the included studies. It has been suggested that large randomised controlled trials (RCT) are required in order to prove beyond doubt the effectiveness of NAc. Thus far three RCT have been conducted that included more than 300 patients.[31-33] Unfortunately, these studies also differed in protocol. The study by Azmus *et al*. is the only in which oral NAc was used and added to a standardised pre- and post-hydration protocol. In contrast, Webb *et al*. used intravenous NAc and incomplete hydration, whereas Marenzi *et al*. used a combination of intravenous and oral NAc in patients that received posthydration only. In two studies no benefit of NAc was observed.[32,33]

In conclusion, there is insufficient evidence to incorporate the routine use of NAc either intravenously or orally on top of an adequate hydration regimen in the guidelines.

Sodium bicarbonate

It has been hypothesised that alkalisation of the urine by administration of sodium bicarbonate reduces pH-dependent renal generation of reactive oxygen species,

Table 2. *Overview of positive trials with N-acetylcysteine (NAc)*

Author (year)	Events in control group N (%)	Events in NAc group N (%)	Remarks
Tepel (2000)[24]	9 (21)	1 (2)	Standard hydration; standard NAc
Shyu (2002)[25]	15 (25)	2 (3)	Standard hydration; NAc 2 dd 400 mg
Diaz Sandoval (2002)[26]	13 (45)	2 (8)	Short hydration; one dose NAc 600 mg orally before procedure
Baker (2003)[27]	8 (21)	2 (5)	Hydration different between groups; NAc 150 mg/kg iv immediately before procedure, 50 mg/kg * 4 hours thereafter
Kay (2003)[28]	12 (12)	4 (4)	Hydration with NaCl 0.9%; standard NAc
MacNeill (2003)[29]	7 (32)	1 (5)	In outpatients short hydration (4 h) and 2 doses of 600 mg NAc within 4 hours before procedure
Ochoa (2004)[30]	11 (25)	3 (8)	Short hydration (150 ml/h * 4 h); NAc 1000 mg orally 1 hour before and 4 hours after procedure
Marenzi (2006)[31]	39 (33)	17 (15)	No prehydration; NAc 600 mg iv before, 2 dd 600 mg after procedure
		10 (8)	No prehydration; NAc 1200 mg iv before, 2 dd 1200 mg after procedure

Standard hydration: NaCl 0.45% 1 ml/kg/h 12 hours before and 12 hours after procedure Standard NAc: 2 dd 600 mg, day before and day after procedure.

a mediator of CIN. The study by Merten *et al*. was the first to confirm the efficacy of sodium bicarbonate in clinical practice.[34] They performed an RCT in patients undergoing an elective diagnostic procedure. Patients were randomised to receive a 154 mEq/l infusion of sodium bicarbonate or sodium chloride intravenously, as a bolus of 3 ml/kg/hour for one hour before the administration of contrast, followed by an infusion of 1 ml/kg/hour for six hours after the procedure. These results were confirmed in several recent studies, which differed in study protocol (*table 3*).[35-37] By contrast, a large retrospective study showed that the use of sodium bicarbonate was associated with an increased incidence of CIN. For obvious reasons data of retrospective studies must be interpreted with caution.[38]

The abovementioned studies (summarised in *table 3*) did not compare sodium bicarbonate to standard hydration. The practical advantage of the less time-consuming sodium bicarbonate regimen is evident. Briguori *et al*. compared sodium bicarbonate according the Merten schedule (which provides 630 ml in a 70 kg patient) with the standard hydration regimen of isotonic saline infused at a rate of 1 ml/kg/hour starting 12 hours before and continuing 12 hours after the procedure (equivalent to 1680 ml).[39] In patients with heart failure the infusion rate of isotonic saline was reduced to 0.5 ml/kg/hour. In addition both groups received NAc orally. The incidence of CIN (>25% increase in serum creatinine) was lower in the bicarbonate group than in the saline group (1.9 *vs* 9.9%; p=0.01). These results seem convincing. However, looked at more closely the study poses some questions. First, the differences in hydration volumes between the saline and bicarbonate group were lower than aimed for (1562 ± 585 *vs* 1081 ± 445 ml). Furthermore, in both groups diuresis was more than 1400 ml/day indicating that all patients were well hydrated.

In conclusion: it remains to be proven, especially in volume-depleted patients, that hydration with sodium bicarbonate according to the Merten schedule is a good substitute for standard hydration with isotonic saline. However, in case of emergency procedures when there is not enough time to prehydrate, sodium bicarbonate infusion according to the Merten schedule is probably superior to a short period of saline infusion.

TOXICITY OF GADOLINIUM CONTAINING CONTRAST MEDIA

The risks of contrast-induced nephropathy associated with the use of iodinated contrast media certainly stimulated the application of contrast-enhanced magnetic resonance imaging (MRI) techniques in patients with renal failure. For MRI techniques gadolinium-containing contrast media are used.

Gadolinium is a heavy metal. Gadolinium is very toxic, and free gadolinium causes severe hepatic necrosis. Therefore, the currently used gadolinium containing

Table 3. *Overview of studies with sodium bicarbonate*

Author (year)	$NaHCO_3$ infusion schedule	Comparator	CIN experimental group	CIN control group	Remarks
Merten (2004)[34]	$NaHCO_3$ 154 mmol/l 3 ml/kg/h *1 hour before 1 ml/kg/h *6 hours after	NaCl 154 mmol/l Same infusion schedule	1/60	8/59	Creat 160 µmol/l No hydration No data on volume status of patients
Briguori (2007)[39]	$NaHCO_3$ cf Merten	NaCl 0.9% 1 ml/kg/h -12 to +12 hours	2/108	11/111	Creat 175 µmol/l All patients received NAc 2 dd 1200 mg Expected infusion volume: NaCl 1800 ml, $NaHCO_3$ 675 ml; Diuresis: NaCl 1703 ml, $NaHCO_3$ 1485 ml Actual infusion volume: NaCL 1562 $NaHCO_3$ 1081 ml
Masuda (2007)[35]	$NaHCO_3$ cf Merten	NaCl 0.9% Similar schedule	2/30	10/29	Creat 115 µmol/l
Recio-Mayoral (2007)[37]	$NaHCO_3$ 154 mmol/l, 5 mg/kg iv * 1 hour before + 2400 mg NAc iv	No prehydration	1/56	12/55	Creat 90 µmol/l All patients received posthydration and 2 dd 600 mg NAc after the procedure
Ozcan (2007)[36]	$NaHCO_3$ 154 mmol/l, 1 ml/kg/hour from -6 hour to + 6 hour	NaCl 154 mmol/l, similar schedule	4/88	12/88	Creat 120 µmol/l Third group received 2 dd 600 mg NAc + saline; no effect CIN 11/88

$NaHCO_3$ = sodium bicarbonate; creat = serum creatinine; NaCl = sodium chloride; NAc = N-acetylcysteine.

contrast media are all chelates, which must ensure that no free gadolinium is present in the circulation. Several chelates are available, which differ in structure and ionic strength (*table 4*). Although the chelates bind gadolinium, some free gadolinium will be present and the amount is dependent on the physicochemical properties of the chelate. Non-ionic linear chelates are less stable than ionic macrocyclic chelates.

Initial studies suggested that gadolinium-containing contrast media were relatively safe. These studies only addressed short-term safety.

Over the past years it has become evident that the use of gadolinium-containing contrast media is associated with the development of a severe, life-threatening side effect, i.e. nephrogenic systemic fibrosis, especially in patients with severe renal failure. This entity was initially described in 2000 as nephrogenic fibrosing dermopathy (NFD) by Cowper *et al.* in dialysis patients. NFD is a skin disorder characterised by thickening of the skin, predominantly involving the limbs.[40] Histologically, the skin lesions consist of irregular bundles of collagen, and an increased number of spindled CD34 positive, fibroblast-like cells. There is no evidence of inflammatory cells or eosinophils. In some patients the disorder not only involved the skin, but also the muscles, diaphragm, and organs. In view of the systemic character, the term nephrogenic systemic fibrosis (NSF) was introduced. NSF was not a benign disorder, in many patients the disease progressed to death.[41] In 2006, a relationship between NSF and the use of gadolinium was suggested.[42,43] Grobner described five haemodialysis patients who developed NSF within two to four weeks after administration of gadolinium-DTPA. Another report by Marckman *et al.* described 13 patients with NSF. All patients had severe renal failure; however, five patients were not yet receiving renal replacement therapy. The first sign of NSF was noted 2 to 75 days after exposure to gadodiamide. A recent case-control study included 19 patients with NSF and confirmed the association of NSF with gadolinium exposure.[44] In a multivariate analysis, exposition to gadolinium was the most independent predictor of the development of NSF. In that study, 18 out of 19 cases had been treated with a gadolinium-containing contrast agent, in four of them the interval between exposure and onset of the disease was more than 12 months. Thus far, more than 400 patients with NSF have been reported.[45,46] More than 95% of the evaluated patients had been exposed to gadolinium within three months prior to the onset of disease. The incidence of NSF in patients with end-stage renal disease exposed to gadolinium is estimated at 2 to 5%.[45,47] A recent study suggests that the incidence may be even higher if limited abnormalities of the skin are also considered.[48] Todd *et al.* carefully studied the skin of a cohort of dialysis patients. The skin was evaluated with respect to hyperpigmentation, hardening and thettering. They observed such changes in 16 of 54 (30%) patients exposed to gadopentetate, and in only one of 36 unexposed patients. The presence of these skin lesions was associated with an increased mortality rate, with an adjusted hazard ratio 2.9. Prince *et al.* most recently reported the incidence of NSF using data from two large medical centres.[49] They observed 15 cases of NSF after 83,121 MRI procedures (0.17%). In all patients a linear chelate was used. The incidence was 0.4% in patients on chronic haemodialysis. NSF occurred more frequently in patients with acute renal failure who received Gd-containing contrast media in the phase of deteriorating renal function (incidence 8.4%). In these patients, when haemodialysis was delayed for more than two days, the incidence of NSF amounted to 19% (11 of 58 patients). The exact mechanism of gadolinium-induced skin fibrosis is unknown, although it is suggested that gadolinium may cause changes in fibroblast characteristics. It is not surprising that patients with kidney failure are at increased risk, since the half-life of the gadolinium-containing chelate is increased in patients with renal failure. Although limited data are available, it is likely that also the dose of the contrast agent is an important issue. This was highlighted in the above-mentioned study by Prince *et al.*[49] NSF only occurred in patients who received more than the standard dose of 0.1 mmol/kg. Most reported cases of NSF have been associated with the use of linear gadolinium

Table 4. *Gadolinium-containing contrast media*[45,48]

Name	Trade name	Structure	Charge	Stability	T1/2	Cases with NSF reported to FDA
Gadodiamide	Omniscan	Linear	Non-ionic	14.9	35 sec	283
Gadoversetamide	Optimark	Linear	Non-ionic	15		20
Gadopentetate-dimeglumine	Magnevist	Linear	Ionic	17.7	10 min	125
Gadobenate dimeglumine	MultiHance	Linear	Ionic	16.9		10
Gadoteridol	ProHance	Cyclic	Non-ionic	16.9	3 hours	9
Gadoterate meglumine	Dotarem	Cyclic	Ionic	18.6	>1 month	NA

Stability is conditional stability, expressed in 10 log. Conditional stability is measure of relationship between free Gd and chelate-bound Gd; high values reflect more avid binding. T1/2 reflects the time to release Gd from the chelate. NSF = nephrogenic systemic fibrosis; FDA = Food and Drug Association.

chelates (*table 4*). Until now, no formal case report has documented the occurrence of NSF after the sole use of a macrocyclic chelate, and only one patient has been reported to the FDA's MedWatch.[46] The lower risk associated with the macrocyclic chelate gadoteridol was confirmed in a cohort study, documenting no evidence of NSF in 141 haemodialysis patients after 198 exposures.[50]

Based on the available evidence, it is evident that linear gadolinium chelates should not be used in patients with a GFR <30 ml/min. Although cyclic compounds appear to be safer, additional data are needed to weigh the benefits and risks of the various imaging techniques

CONCLUSIONS

The use of iodinated contrast media is associated with nephrotoxicity, especially in patients with risk factors such as renal failure, vascular disease and diabetes. Risk can be reduced by identification of high-risk patients and proper management, with hydration being the optimal preventive strategy. In case of an emergency procedure, when there is insufficient time to prehydrate, a short infusion protocol with sodium bicarbonate is preferable. There is a lack of evidence to support the use of oral or intravenous N-acetylcysteine or iso-osmolar contrast media.

Nephrogenic systemic fibrosis is a life-threatening complication of the use of gadolinium-containing contrast media in patients with renal insufficiency. Linear gadolinium chelates should not be used in patients with an eGFR <30 ml/min. In patients with eGFR between 10 and 30 ml/min the small chance of NSF with macrocyclic gadolinium-containing chelates must be balanced against the high risk of developing CIN, and the morbidity and mortality associated with the start of dialysis, the use of intravenous catheters etc. In patients without residual renal function the small chance of developing NSF after cyclic Gd-enhanced MRI imaging may tip the balance to the use of iodine containing contrast media. In patients with end-stage renal disease it is advised to perform haemodialysis within three hours after gadolinium administration and repeat this after 24 hours. As the knowledge on Gd-induced toxicity is evolving quickly, it is important to check the literature on this topic regularly. Recent guidelines can be found at www.esur.org.

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