ORIGINAL RESEARCH

No Increased Risk for Contrast-Induced Nephropathy after Multiple CT Perfusion Studies of the Brain with a Nonionic, Dimeric, Iso-Osmolal Contrast Medium

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BACKGROUND AND PURPOSE: Contrast-induced nephropathy (CIN) is one of the most common causes of in-hospital acute renal failure. The aim of this study was to assess the risk for CIN after repeated administration of the nonionic, dimeric, iso-osmolal contrast agent iodixanol regardless of pre-existing renal function. Changes in serum creatinine (SCr) levels were compared with those of control subjects who did not receive iodinated contrast media (CM).

MATERIALS AND METHODS: Between January 2005 and March 2007, a total of 100 consecutive patients were prospectively included. Patients underwent a CT perfusion (CTP) study of the brain from clinical signs of acute cerebral infarction. CTP was performed with an intravenous bolus of 60 mL of iodixanol-270. Precontrast and postcontrast SCr levels were obtained, and the CTP study was repeated within 32 hours and postcontrast SCR was assessed. The control group consisted of 100 patients scheduled for plain cranial CT examination, who were not exposed to iodinated CM.

RESULTS: Mean baseline SCr level was 0.96 ± 0.35 mg/dL in the contrast group and 1.14 ± 0.74 mg/dL in the control group. After repeated administration of CM, a total of 7 patients had a relative increase of greater than or equal to 25% compared with baseline. In the control group, a relative increase of 25% or more was seen in 12 patients. The difference in the incidence of the rise in SCr of >25% was not significantly different ($P = .094$).

CONCLUSION: Multiple contrast-enhanced studies with intravenously administered iodixanol are not associated with a higher risk for CIN compared with a control group receiving no CM.

With increased use of contrast media (CM), interest in contrast-induced nephropathy (CIN) has risen considerably in recent years. CIN continues to be one of the most common causes of hospital-acquired acute renal failure[1] and is associated with increased morbidity and mortality, especially when hemodialysis is required.[2] The effects of CM are compounded by increased comorbidities in patients receiving them, including pre-existing renal impairment with or without concurrent diabetes, the use of drugs that affect renal function, advanced age, and the use of large volumes of CM.[3]

CIN is an acute decline in renal function occurring after intravascular contrast administration and the absence of an alternative cause.[4,5] CIN has been variably defined: a postcontrast increase in serum creatinine (SCr) levels of at least 0.5 mg/dL or of more than 25% above precontrast values.[6,7] In most cases, the increase in SCr levels occurs within 24 to 48 hours of the administration of the iodinated contrast agent and normally returns to or near the baseline value within 7 days.[4,6,8] The pathophysiology of CIN is not completely understood, but the literature indicates that a reduction in renal perfusion from a direct effect of CM on the kidney and toxic effects on the tubular cells are the main cause.[5] Mechanisms responsible for the reduction in renal perfusion involve vascular and tubular effects (eg, increase in intratubular pressure and tubular obstruction).[9] Characteristics of CM, such as osmolality[10,11] or chemical composition,[12] might influence the risk for CIN. The route of administration may also contribute to the pathogenesis of CIN.[13]

The Nephrotoxic Effects in High-Risk Patients Undergoing Angiography (NEPHRIC) study documented that iso-osmolal CM (IOCM) may have better renal tolerance than low-osmolar CM (LOCM) in high-risk patients undergoing angiography.[14] This has influenced several guideline recommendations that a high risk for the development of CIN be considered one of the indications for the use of LOCM or IOCM.[5,15] Many studies have evaluated the renal safety of the nonionic IOCM iodixanol or that of the other nonionic LOCM in patients with impaired renal function[16-22] but only after intra-arterial contrast injection. Only 3 studies have compared the nephrotoxicity of the dimeric IOCM iodixanol with monomeric CM after intravenous injection.[23-25] These studies indicate a very low risk for CIN after intravenous injection of iodixanol. Petrik et al[26] reported no detectable nephrotoxic adverse effect after a single administration of a maximal of 80 mL of iodixanol regardless of pre-existing renal function.

In a review of published guidelines, Thomsen and Morcos[27] in 2006 reported that most authors advocate the use of the IOCM iodixanol for patients with renal insufficiency. Most guidelines recommend avoiding multiple examinations with iodinated CM in a short period.[27] No published study in the literature evaluates the renal safety of a double administration of iodixanol in patients undergoing contrast-enhanced CT examinations regardless of the pre-existing renal function.

We compared changes in SCr levels on days 3 and 7 in 100 consecutive patients after a double administration of 60 mL of

Received September 20, 2007; accepted after revision March 31, 2008.

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DOI 10.3174/ajnr.A1164

Table 1. Demographic data of patients and control subjects

Data	Iodixanol Group	Control Group	*P* Value
Patients			
Men	52	52	
Women	48	48	
Mean age (years ± SD)	65.4 ± 13.9	67.1 ± 16.5.2	
Mean baseline SCr (mg/dL)/(μmol/L ± SD)	0.96 ± 0.35/85 ± 31.11	1.14 ± 0.74/101 ± 65.4	.082
Risk factors for CIN			
Pre-existing renal impairment (see Table 2)	7	13	.071
Hypertension	68	57	.072
Diabetes mellitus	41	46	.088
Coronary artery disease	56	50	.239
Hypercholesterolemia	55	51	.335
Hyperuricemia	2	0	.249
Diuretics	5	7	.197
Concomitant use of diuretic and ACE inhibitor	5	7	.197
Nephrotoxic drugs (eg, NSAIDs)	12	8	.240

Note:—CIN indicate contrast-induced nephropathy; ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs; SCr, serum creatinine.

iodixanol for CT perfusion studies of the brain within 48 hours with changes in SCr levels of in-hospital patients who were not exposed to an iodinated contrast agent.

Materials and Methods

The local institutional review board approved the study protocol, and we obtained written informed consent from all patients. Between January 2005 and March 2007, a total of 100 consecutive patients were included in the study. The patients were referred by our in-house stroke unit. Patients with clinical signs of acute cerebral ischemia first undergo plain cranial CT examination, which is followed by a contrast-enhanced CT perfusion study (CTP) of the brain if results of the plain scan show no early signs of ischemic infarction or hemorrhage. Precontrast SCr samples were obtained on admission, but CM was administered without knowledge of these values or of any information on the pre-existing renal function, either by the referring physician or by the radiologist. Patients were ineligible for the study if they had known hypersensitivity to iodine-containing contrast agents, hyperthyroidism, or thyroid malignant tumors. Also, nursing and pregnant patients were excluded, as were patients scheduled to receive any medication to prevent CIN or patients undergoing hemodialysis. Comorbidities such as diabetes and hypertension—as potential risk factors for CIN—were initially not registered because contrast administration in the clinical setting of stroke was performed regardless of pre-existing renal function. Possible risk factors influencing CIN[10,22,27] were then evaluated retrospectively by analysis of the patient medical records.

Initially, plain cranial CT examination was performed. In the absence of intracranial hemorrhage or early signs of ischemic infarction, CTP was performed at the level of the basal ganglia. CTP was performed after administration of an intravenous bolus of 60 mL of iodixanol-270 with a flow of 6 mL/s. Previous CTP blood samples were obtained for the precontrast SCr and first postcontrast SCr levels. Plain cranial CT and CTP examinations were repeated within 48 hours of the first examination. The third blood sample was obtained 72 hours after the second administration of the contrast agent.

The patients were encouraged to drink plain mineral water within normal limits after each contrast administration. Volume supplementation was given according to good clinical practice for each patient for whom it was deemed clinically necessary or desirable.

The control group consisted of 100 consecutive patients who were referred by the emergency department for a plain cranial CT examination to exclude intracranial hemorrhage due to the mechanism of their injury. These patients were not exposed to an iodinated contrast agent. Blood samples were obtained for baseline SCr on admission and for follow-up SCr within 48 hours and 72 hours after contrast administration. Patients were ineligible for the control group if acute cerebral ischemia was suspected or if they received iodinated CM during their stay in hospital.

We expressed the results as mean ± SD. We analyzed the changes in SCr using a Wilcoxon signed-rank sum test and the incidence of CIN in both groups using the 2-sided Fisher exact test. Probability values of less than .05 were considered to be significant.

Results

Between January 2005 and March 2007, a total of 100 consecutive patients were included. Table 1 presents the demographic data of these patients. SCr levels were evaluated in all patients before the first administration of iodixanol-270. All patients received the second dose of iodixanol within 32.4 hours. Predose SCr levels were 0.96 mg/dL ± 0.35 mg/dL (85 ± 31.11 μmol/L).

In total, 7 (7%) patients had a baseline SCr level of of greater than or equal to 1.5 mg/dL (Table 2). These patients are at a higher risk regarding CIN, but there was no decline in renal function after the first or second administration of contrast medium in these patients. In the control group, 13 patients had a baseline SCr of 1.5 mg/dL or more (Table 2). The difference was statistically not significant ($P = .071$). One of the patients with elevated baseline SCr levels in the control group had a decline in renal function. There was no difference in baseline SCr values between both groups ($P = .082$).

Possible risk factors influencing CIN were retrospectively evaluated. Their incidence between both groups was not significant (Table 1).

After the first administration of the contrast agent, no absolute increase of 0.5 mg/dL or more was seen, and a relative increase of 25% or more was observed in 1 patient (1%). Mean SCr level after the first contrast injection was 0.84 ± 0.30 mg/dL (74 ± 26.13 μmol/L). There was a decrease in mean SCr level of 11.06% relative to the baseline SCr level.

Perfusion CT examination was repeated 32 ± 4.3 hours after admission. After the second administration of iodixanol, an absolute increase 0.5 mg/dL or more compared with the

Table 2. SCr of patients with elevated baseline SCr Greater than or equal to 1.5 mg/dL

Patient No.	Baseline SCr (mg/dL)	First Postcontrast SCr (mg/dL)	Second Postcontrast SCr (mg/dL)
Control Group			
2	1.67	1.76	2.04
6	1.61	1.35	1.17
15	1.54	0.67	1.07
28	4.97	5.21	3.90
29	4.04	4.59	4.77
39	2.74	2.70	2.81
41	2.13	2.14	2.09
55	2.02	1.31	1.48
57	2.50	1.98	2.78
67	2.73	2.14	2.57
74	3.29	2.88	3.43
76	2.08	2.16	2.73
78	1.98	0.76	1.50
Patient Group			
54	1.66	1.33	1.41
57	1.86	1.44	1.06
69	1.76	1.43	1.62
74	1.63	1.62	1.70
81	1.72	1.48	1.72
78	1.56	1.37	1.69
85	2.87	1.90	1.20

Note:—SCr indicates serum creatinine.

Table 3. SCr in the iodixanol and control group

	Iodixanol Group	Control Group
Mean baseline (mg /dL ± SD)	0.96 ± 0.35	1.14 ± 0.74
Minimum baseline (mg/dL)	0.45	0.41
Maximum baseline (mg/dL)	2.8	4.97
Mean first postcontrast SCr (mg /dL ± SD)	0.84 ± 0.3	1.07 ± 0.77
Minimum first postcontrast (mg/dL)	0.37	0.29
Maximum first postcontrast (mg/dL)	1.9	5.21
Mean second postcontrast SCr (mg/dL ± SD)	0.84 ± 0.31	1.11 ± 0.76
Minimum second postcontrast (mg/dL)	0.37	0.37
Maximum second postcontrast (mg/dL)	1.72	4.77

Note:—SCr indicates serum creatinine.

first postcontrast SCr level was not observed. A relative increase of 25% or more occurred in 8 patients.

Postcontrast SCr level after double administration of 60 mL iodixanol (total amount of iodine 32.4 g) was 0.84 ± 0.31 mg/dL (75 ± 26.97 μmol/L) (Table 3). Blood samples for the second postcontrast SCr level were obtained 70.64 ± 2.02 hours after the second PCT. In the patient with a relative increase 25% or more after the first administration of CM, SCr levels remained stable after the second dose, with only a slight increase of 7.02%.

Overall, an absolute increase of 0.5 mg/dL or more of SCr level after double administration of iodixanol was not observed. One (1%) patient had a relative increase of 25% or more after the first contrast dose, but SCr level remained stable after the second CM administration.

In 6 of the 8 patients with a relative increase of 25% or more after the second CM dose compared with the first postcontrast SCr level, the increase was less than 25% compared with baseline SCr level, because SCr values dropped below the precontrast levels after the first CM administration.

Table 4. Patients with contrast-induced nephropathy

Patient No.	Baseline SCr (mg/dL)	First Postcontrast SCr (mg/dL)	Second Postcontrast SCr (mg/dL)
Control Group			
12†	1.00	1.04	1.38
20†	0.69	0.80	0.87
22†	0.40	0.44	0.60
29*,‡	4.04	4.59	4.77
43†	1.30	1.53	2.19
46†	0.48	0.76	0.79
60†	0.88	1.10	1.22
61†	0.84	1.28	1.92
63†	1.06	1.00	1.38
73†	1.32	1.30	1.73
75†	0.79	0.94	1.11
76†,*	2.08	2.16	2.73
Patient Group			
30†	0.51	0.58	0.66
42†	0.94	1.29	1.38
47†	0.71	0.64	0.89
48†	0.63	0.58	0.88
58†	1.11	1.13	1.39
70†	0.58	0.67	0.79
83†	0.62	0.75	0.86

Note:—SCr indicates serum creatinine
*, increase of greater than or equal to 0.5 mg/dL
†, increase of greater than or equal to 25%
‡, elevated baseline SCr.

There were 4 (4%) patients who did not have a relative increase of 25% or more after each CM administration, but the overall increase was 25% or more compared with baseline (Table 4). This led to an overall incidence of CIN of 7%.

In 6 of these 7 patients with CIN, SCr levels returned to normal limits on follow-up examinations after a mean of 9.3 days (range, 7–13 days). Follow-up SCr levels were not available in 1 patient.

The demographic data of the control group are summarized in Table 1. Mean SCr level of the control group on admission was 1.14 ± 0.74 mg/dL (101 ± 65.44 μmol/L). After 33 ± 6.7 hours in hospital, SCr level was 1.07 ± 0.77 mg/dL (95 ± 68.10 μmol/L). There were 7 (7%) patients who experienced an increase in SCr levels of greater than or equal to 25% above the baseline and another who had an absolute increase of 0.5 mg/dL or more. In 4 of these cases, SCr levels returned to baseline. SCr level was 1.11 ± 0.76 mg/dL (98 ± 67.48 μmol/L) after 105.8 ± 3.32 hours in hospital (72.8 ± 1.30 hours after the second SCr level measured) without exposure to an iodinated contrast agent (Table 3). In 13 cases, there was an increase in SCr levels of greater than or equal to 25% above the second SCr measured. In 6 of these patients, a relative increase of 25% or more also meant an absolute increase in 0.5 mg/dL or more.

Overall, an absolute increase of greater than or equal to 0.5 mg/dL above baseline levels was seen in 1 (1%) patient. This patient already had elevated baseline SCr levels; therefore, the absolute increase corresponded to a relative increase of 13.8%. SCr levels remained stable in this patient with only a slight increase of 0.18 mg/dL (3.94%) from the second to the third SCr values measured (Table 4).

In 7 of the 13 patients with a relative increase of the second SCr levels of 25% or more compared with the first SCr levels, the

Table 5. Clinical studies with intravenous LOCM

Study	Year of Publication	Contrast Medium	No. of Subjects	Criterion for CIN	Outcome
Barrett[23]	2006	Iopamidol, Iodixanol	153	increase ≥0.5 mg/dL in SCr	CIN in 3% (2 subjects) of iodixanol-group
Becker[37]	2005	Iodixanol	100	>0.5 mg/dL increase in SCr	CIN in 9%
Kolehmainen[25]	1998	Iobitridol, iodixanol	50	≥0.5 mg/dL increase in SCr	CIN in 4 of 25 subjects in each group
Tepel[32]	2000	Iopromide	83	≥0.5 mg/dL increase in SCr	CIN in 21% without NAC
Carraro[24]	1998	Iopromide, iodixanol	64	≥50% increase in SCr	CIN in no subject who received LOCM and in 3% (2/32) with IOCM

Note:—SCr indicates serum creatinine; CIN, contrast-induced nephropathy; LOCM, low osmolar contrast medium; IOCM, iso-osmolal contrast medium; NAC, *N*-Acetylcystein.

increase was less than 25% compared with baseline SCr levels, because SCr dropped below the first SCr values measured.

Two (2%) patients did not have a relative increase of 25% or more for each SCr level measured, but the overall increase was 25% or more compared with baseline (Table 4). This led to an overall incidence of CIN in 12 (12%) patients.

The difference between the incidence of the rise of SCr above the levels of CIN in both groups was not significant ($P = .094$) either for a relative increase of 25% or more or an absolute increase of greater than or equal to 0.5 mg/dL above baseline.

Discussion

The hypothesis that intravascular administration of an iodinated contrast agent can cause renal dysfunction is generally accepted. The incidence of CIN has been reported to range from less than 1% to greater than 30%.[13] Iodinated contrast agents are cited as one of the leading causes of acute renal function failure in hospitalized patients.[10,28] It has been suggested that the nephrotoxicity of iodinated contrast agents is a function of dose in relationship to the level of renal function at the time of injection. The risk for acute renal dysfunction is believed to be proportional to the level of any pre-existing renal failure and to be increased in patients with longstanding diabetes mellitus.[29] Therefore, many radiology departments routinely require determination of SCr levels in all patients before administration of an iodinated contrast agent. However, this may not be practical in many institutes, and, in the emergency department, SCr measurements may cause unacceptable delays in diagnostic imaging, especially in the clinical setting of stroke with treatment options depending on the results of the CTP study.

There are numerous publications of patient series receiving iodinated contrast material and subsequently experiencing an increase in SCr levels, thus supporting the concept of CIN.[24,30-32] However, the risk for CIN is believed to be overestimated because of the absence of control groups in most of the published series and the comparison of the nephrotoxicity caused by contrast agents administered by different routes.[29,33-35]

To our knowledge, this is the first study on the renal safety of repeated intravenous administration of the IOCM iodixanol, though most guidelines recommend avoiding multiple examinations with CM.[5] The results of our study do not demonstrate any difference in the incidence of acute renal failure between patients receiving 60 mL of iodixanol twice intravenously with a total amount of 32.4 g iodine regardless of their pre-existing renal function and a control group receiving no contrast agent.

Most studies on the nephrotoxicity of iodixanol compare the nonionic dimeric IOCM with nonionic monomeric LOCM, only a few after intravenous injection[23-25,36] and most of them after intra-arterial injection.[16-21,36] Intra-arterial injections are mainly used for coronary procedures, but especially cardiac catheterization may impose or cause many conditions that have the potential to diminish renal perfusion and produce an increase in SCr levels, which may erroneously be ascribed to the contrast medium itself.[29] McCullough[11] reported in 2006 lower rates of CIN and smaller increases in SCr levels after intra-arterial injection of iodixanol in a meta-analysis of renal safety of iodixanol compared with LOCM.

Becker and Reiser[37] assessed SCr levels in patients with renal impairment on days 3 and 7 after intravenous administration of 100 mL of iodixanol for CT angiography (Table 5). CIN was observed in 9 (9%) patients, and in 7 of these patients, renal function normalized by day 7. In that study, a higher amount of iodine was administered in a single dose, but the total amount of iodine was higher in our study. Nevertheless, the incidence of CIN was lower in our group.

In the study by Kolehmainen and Soiva [25] study, CIN developed in 4 of 25 subjects who received a nonionic, monomeric LOCM versus 4 in 25 subjects who received iodixanol. Differences were not significant. The incidence of CIN in the Kolehmainen and Soiva[25] study was much higher than in our group. This may be from a selection bias because only patients with severe renal impairment were included by the authors.

Petrik et al[26] (coworkers from our group) performed a prospective study with 138 patients who underwent a CT perfusion study of the brain with different amounts of iodixanol (total amount of iodine 6 g to 25 g) regardless of pre-existing renal function.[26] SCr was measured before contrast administration and on days 3 and 7. CIN was not observed in any patients and changes in SCr were not significant. Although there was no control group in their study, the results are consistent with our data. We observed no significant differences in changes in SCr levels between the contrast and control group in CIN.

In a literature analysis of studies investigating renal safety of CM, Rao et al[29] reported in 2006 that patients received the CM intravenously only in a minority of recent studies, and only 5% of these studies had a control group with subjects who received no CM.

Cramer et al[38] performed a comparative study of the nephrotoxicity of high-osmolar CM (HOCM) versus a control group who received no CM. Renal impairment in this study was defined as a maximum increase of 50% over the baseline SCr or greater than or equal to 0.5 mg/dL. The difference in renal dysfunction was not significant, with 2.1% in the contrast group and 1.3% in the control group. There may be a selection bias in the control group of this study because the decision to perform unenhanced CT may have been influenced by the perceived risk for CIN. As

HOCM are believed to be more nephrotoxic than LOCM or IOCM,[12] caution is in order when comparing the results of this study with our study.

Heller et al[39] assessed the possibility of CIN after the administration of HOCM, LOCM, and in patients who received no CM. Patients in the control group were selected for the risk for CIN. The difference in renal impairment between the 3 groups was also not significant. Both articles clearly demonstrate that the CIN risk is not significantly increased after intravenous administration. This finding is consistent with our results.

In contrast to Cramer[38] and Heller,[39] there is no selection bias in our control group because the contrast agent was administered regardless of pre-existing renal function, and patients were included into our study on the basis of clinical criteria without the knowledge of baseline SCr level. Patients were only excluded of they were undergoing hemodialysis or were scheduled to receive any medication to prevent CIN. Also, the kidneys were exposed twice to CM within 48 hours.

Patients in the control group were scheduled for plain cranial CT examination by the emergency department to exclude intracranial hemorrhage from their mechanism of injury to the head. The incidence of acute decline in renal function and the variability of SCr levels in the control group demonstrate that in any series of patients who are ill, some will experience renal failure. Variability of SCr levels in the control group reflects the possibility of random variation in SCr levels because hospitalized patients are likely to have concurrent conditions that might affect renal function.[40] The incidence of increased SCr above the levels of CIN was statistically not different between the control group and the subjects receiving CM ($P = .094$). Therefore, increases in SCr levels after CM administration may have other causes than the CM themselves, especially in patients who are ill.

Conclusion

Multiple contrast-enhanced studies with intravenously administered iodixanol are not associated with a higher risk for contrast-induced nephropathy compared with a control group receiving no CM.

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