Radiographic Contrast Agents, Drugs Useful for Diagnostics, but with Contrast-Induced Nephropathy as Side Effect

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Abstract

Iodinated radiographic contrast agents are drugs very useful in clinical practice to improve the visibility of internal organs and structures in X-ray based imaging techniques. Their use keeps increasing, particularly in less healthy and older patients, with one or more comorbid conditions, such as advanced vascular disease, severe long-standing hypertension, diabetes and impairment of renal function. However, they may have side effects the most frequent being Contrast-Induced Nephropathy (CIN). After a short description of the epidemiology and pathogenesis of CIN, the conditions favoring the development of CIN in patients are discussed, the main ones being pre-existing renal impairment, particularly if secondary to diabetic nephropathy, salt depletion and dehydration, congestive heart failure, age greater than 70 years and concurrent use of nephrotoxic drugs. Then the measures to prevent CIN are suggested, beginning with monitoring renal function, discontinuation of potentially nephrotoxic drugs, use of either iodixanol or iopamidol at the lowest dosage possible. The main procedure for prevention of CIN is an adequate hydration of the patient with either oral water intake or isotonic sodium chloride or sodium bicarbonate infusion. (A long list of references is provided that will enable readers a deep evaluation of the topic).

Keywords

Contrast-Induced Nephropathy; Contrast-Induced Acute Kidney Injury; Acute Renal Failure; Radiographic contrast media; Iodinated contrast material; Renal cell injury

Abbreviations

IRCA: Iodinated Radiographic Contrast Agents; CIN: Contrast-Induced Nephropathy; CI-AKI: Contrast-Induced Acute Kidney Injury; CT: Computed Tomography; MDRD: Modification of Diet in Renal Disease; eGFR: Estimated Glomerular Filtration Rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration;

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LOCM: Low-Osmolar Contrast Media; NO: Nitric Oxide; ROS: Reactive Oxygen Species; HOCM: High-Osmolar Contrast Media; IOCM: Iso-Osmolar Contrast Media; ARF: Acute Renal Failure; SCR: Serum Creatinine; RBF: Renal Blood Flow; CRF: Chronic Renal Failure; ACE: Angiotensin-Converting Enzyme inhibitors; ARBs: Angiotensin II Receptor Blockers; NaC: N-acetylcysteine; KDIGO: Kidney Disease Improving Global Outcomes; ERBP: European Renal Best Practice

Iodinated radiographic contrast agents (IRCA) are very useful drugs to improve the visibility of internal organs and structures (iodine is an important component of contrast media possessing high-contrast density) in X-ray based imaging, techniques such as radiography, angiography and contrast-enhanced computed tomography (CT) scans, and to perform cardiac catheterizations and percutaneous coronary interventions. IRCA have been in use for over 60 years and their use for imaging and intravascular intervention keeps increasing, particularly in less healthy and older patients, with one or more comorbid conditions [1].

IRCA may have side effects, sometimes just mild inconvenience such as itching, in rare cases a life-threatening emergency [2]. Among the side effects associated with the use of intravenous or intra-arterial injection of IRCA, contrast-induced nephropathy (CIN) is undoubtedly the most important and frequent well known adverse reaction [3].

**Contrast-Induced Nephropathy (CIN)**

We define CIN as an Acute Renal Failure (ARF) occurring 24-72 hours after the exposure to intravenous injection of IRCA that cannot be attributed to other causes.

It is usually a non-oliguric ARF with asymptomatic transient decline in renal function, peaking on the third to fifth day, and returning to baseline within 10-14 days [4]. It is mirrored by an absolute (0.5 mg/dL or greater) or relative (by 25% or greater) increase in serum creatinine (SCr) from baseline or, better, by a decrease (to 30-60 mL/min - renal insufficiency – or less) in the estimated glomerular filtration rate (eGFR), i.e. the creatinine clearance calculation using either the MDRD (Modification of Diet in Renal Disease) calculation [5] or the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [6], or alternatively by the very simple Cockcroft-Gault formula [7].

CIN may also be referred to as Contrast-Induced Acute Kidney Injury (CI-AKI). In some cases, CIN may cause a more severe impairment of renal function with oliguria (<400 mL/24 hrs), requiring dialysis. In these cases the mortality is high.

The clinical feature and the management of CIN are the same as that for ARF due to other causes [8-10].

CIN occurs in up to 5% of hospitalized patients who exhibit normal renal function prior to the injection of contrast medium [11] and in about 2% [1] or even 1% of outpatients with eGFR >45 mL/min per 1.73 m² [12].

Thus, CIN is uncommon in patients with normal pre-existing renal function [13]. It occurs more frequently in patients with renal impairment, particularly those with diabetic nephropathy [14]. Among all procedures utilizing contrast agents for either diagnostic or therapeutic purposes, coronary angiography and percutaneous coronary interventions are associated with the highest rates of CIN [15]. This is mainly related (A) to intra-arterial injection: IRCA seem to be more nephrotoxic when given intra-arterially because of the higher acute intrarenal concentration [16,17], particularly if the arterial injection is suprarenal [18-24]; (B) to the high dosage of the contrast used and (C) to the type of patients who are usually in advanced age, with one or more comorbid conditions, such as advanced vascular disease, severe long-standing hypertension, diabetes and some renal function impairment [25,26].

In a retrospective study on 11,588 patients undergoing CT either without contrast or with the low-osmolar contrast medium iohexol or the iso-osmolar contrast medium iodixanol, Bruce et al [27] observed that the incidence of CIN in the low-osmolar contrast medium group was similar to that of the control group up to an SCr level of 1.8 mg/dL; but an SCr above 1.8 mg/dL was associated with a higher incidence of CIN in the low-osmolar contrast medium group.

In another retrospective study performed in 20,242 adult inpatients undergoing computed tomography (CT) (10,121 untreated and 10,121 receiving i.v. IRCA), Davenport et al [28] found that i.v. low-osmolarity IRCA injection is a risk factor for nephrotoxicity in patients with a stable eGFR <30 mL/min/1.73 m²; no nephrotoxicity was observed in patients with a pre-CT eGFR >45 mL/min/1.73 m². The Authors concluded that i.v. IRCA is a nephrotoxic risk factor, but not in patients with a stable SCr <1.5 mg/dL or eGFR >45 mL/min/1.73 m² [28].

We must admit, however, that some Authors do not believe that IRCA are responsible for impairment of renal function. Thus, McDonald et al [29] carried out a retrospective study to determine the causal association and effect of IRCA exposure on the incidence of CIN. All abdominal, pelvic, and thoracic CT...
Phenomenology of CIN

The mechanisms of nephrotoxicity by IRCA are quite complex and not fully understood [30]. Many factors are involved, including an initial increase followed by a more prolonged decrease in renal blood flow (RBF), a decrease in nitric oxide (NO), medullary vasoconstriction and severe reduction in medullary blood flow with renal ischaemia, severe medullary hypoxia, intracellular Ca++ overload, direct tubular damage, formation of reactive oxygen species (ROS) [31-36], increased intratubular pressure secondary to contrast-induced diuresis, increase of tubular fluid viscosity, tubular obstruction and finally a decrease in GFR [37].

In vivo experiments in rats have demonstrated that the decrease in cortical and medullary blood flow induced by IRCA is partly accounted for by the downregulation of endogenous renal cortical and medullary NO synthesis [38]. The use of the superoxide dismutase (SOD) mimetic Tempol reduced iodixanol-induced vasoconstriction [39]. A recombinant manganese SOD administered in vivo to rats undergoing diatrizoate treatment caused an improvement in GFR and a reduction in renal histologic damage [40].

IRCA have also a direct toxicity on tubular epithelium and on endothelial cells. In vitro cell culture studies have shown that all IRCA cause a decrease in cell viability [41-45] and changes in morphology [46,47]. Endothelial damage by iodixanol was also noted by Sendeski et al [48] using isolated human and rat descending vasa recta. The biochemical changes underlying these effects have been extended to studying changes in major intracellular signalling pathways involved in cell survival, death and inflammation [43-45,49-52] in cultured primary human renal tubular cells [53,54]. IRCA cause alteration of mitochondrial enzyme activity and apoptosis of renal tubular cells [54-60].

Recent work has shown that contrast media affect the membrane skeleton of erythrocytes, with iopromide causing drastic changes in the band3-spectrin network that may contribute to microcirculatory disorders and gas transport, contributing to tissue hypoxo-oxygenation [61].

The iodinated radiographic contrast agents (IRCA)

IRCA have different osmolalities and different viscosities (Table). The ionic High-Osmolar Contrast Media (HOCM, e.g. diatrizoate) have an osmolality between 1500 and 1800 mOsm/kg, 5 to 8 times the osmolality of plasma. Nonionic Low-Osmolar Contrast Media (LOCM e.g. iohexol) have an osmolality between 600 and 850 mOsm/kg, 2–3 times the osmolality of plasma. Nonionic Iso-Osmolar Contrast Media (IOCM e.g. ioxidanol) have an osmolality of 290-300 mOsm/kg, the same osmolality as plasma [37,62].

HOCM have a greater cytotoxic effects on proximal tubular cells in vitro than do LOCM or IOCM. At equal iodine concentrations (300 mg I/mL), the HOCM ioxithalamate showed stronger cytotoxic effects than did other IRCA [42]. The use of LOCM rather than HOCM is beneficial in reducing the incidence of CIN in patients with pre-existing renal failure [63-66]. Thus, the HOCM are used less frequently. There is no difference in the cytotoxicity of LOCM iomeprol and IOCM iodixanol at equal iodine concentrations in renal proximal tubular cells in vitro [67]. Recent studies and meta-analyses have shown no significant difference in the incidence of CIN between IOCM and LOCM [67-70] with the exception of LOCM iohexol that is more nephrotoxic [63,71]. However, in a study of Nguyen et al [72] involving 117 patients (83 men, 34 women; mean age, 64 years; range 18-86 years) with an impaired renal function, even if the differences between the two compared agents (iodixanol and iopromide) was not drastic, fewer patients in the iodixanol group (8.5% versus 27.8%) had an increase in serum creatinine of 0.5 mg/dL (or more) and a reduction in GFR of 5 ml/min (or more) (42.3% versus 24.1%).

IRCA have different viscosities (Table). The low osmolality achieved with the IOCM has been obtained at the price of increased viscosity; at comparable iodine concentrations and x-ray attenuation, the non-ionic dimeric IOCM have about twice the viscosity of non-ionic monomeric LOCM [73-75].

Patient conditions favoring the development of CIN

According to the European Society of Urogenital Radiology pa-
tient conditions favoring CIN are represented by pre-existing renal impairment particularly when associated with diabetes mellitus, salt depletion and dehydration, congestive heart failure, an age greater than 70 years and concurrent use of nephrotoxic drugs [76,77].

The worst condition is a pre-existing impairment of renal function, irrespective of cause. The incidence of CIN in patients with chronic renal failure (CRF) ranges from 14.8 to 55% [15]. The lower the eGFR, the greater is the risk of CIN. An eGFR of 60 ml/min/1.73m² is a reliable cutoff point for identifying patients at high risk for the development of CIN [4]. Diabetes mellitus is the second most important condition, particularly when associated with renal insufficiency [78]. At any given degree of baseline eGFR, diabetes doubles the risk of developing CIN. The incidence of CIN in diabetic patients varies from 5.7 to 29.4% [15,79]. The concomitant use of nephrotoxic drugs such as aminoglycosides, cyclosporin A, amphotericin, cisplatin and nonsteroidal anti-inflammatory drugs is another condition favoring CIN [81,82].

The role of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) in the incidence of CIN is still controversial [78]. Many Authors suggest to discontinue these drugs in patients with CRF [80,83-88]. Others deny such a procedure [89]. KDIGO does not suggest to discontinue these medications prior to contrast administration [90].

Other conditions favouring CIN include prolonged hypotension [16,91], severe dehydration, reduction of ‘effective’ intravascular volume due to congestive heart failure, liver cirrhosis, or salt depletion secondary to abnormal fluid losses associated with insufficient salt intake [16,34,91-93].

Dehydration and salt depletion deserve a special discussion. Dehydration is the decrease of body water, as it occurs sometimes in old patients due to impaired sensation of thirst [93]. But the term dehydration is frequently used to indicate salt and water depletion. Dehydration and salt depletion are responsible for the reduction of the ‘effective’ circulating blood volume, i.e. the relative fullness of the arterial tree as determined by cardiac output, peripheral vascular resistance and total blood volume [9]. A reduction of the ‘effective’ circulating blood volume may be due to congestive heart failure, compromised left ventricle systolic performance, prolonged hypotension, liver cirrhosis, nephrotic syndrome or salt depletion.

**Measures for prevention of CIN**

The first general rule is that in any patient undergoing any radiographic procedure, renal function has to be measured before and after the procedure; in patients at high risk of CIN these parameters should be monitored before and once daily for 5 days after the use of IRCA [16,94].

The second measure is that potentially nephrotoxic drugs (aminoglycosides, vancomycin, amphotericin B, metformin and nonsteroidal anti-inflammatory drugs) should be discontinued before the IRCA injection [94]. For aminoglycosides the ERBP [95] suggests to not using more than one shot of aminoglycosides for the treatment of infections in patients with normal kidney function in steady state, and that the drugs should be administered as a single daily dose rather than multiple-dose, with their levels monitored. Metformin, an oral antihyperglycemic drug used to treat type II diabetes, stimulates intestinal production of lactic acid; a severe lactic acidosis that can be fatal may occur in case of renal failure, since the drug is excreted unchanged almost entirely by the kidneys. Thus, metformin should be discontinued at least 12 hours before the IRCA injection and not be resumed for a minimum of 36 hours after the procedure (or longer if the SCr has not returned to baseline) [96].

The third measure is the choice of the least nephrotoxic radiographic contrast agent. Iodixanol (IOCM) and iopamidol (LOCM) appear to be contrast agents of choice to reduce risk of CIN [97]. The fourth measure is to use the lowest dosage possible of IRCA. High doses of IRCA are required in coronary angiography and percutaneous coronary intervention. For these procedures, some formulas have been suggested to calculate the least dangerous dosage [94]:

(A) Cigarroa’s formula [98]: 5 mL of contrast per kg b.w./SCr (mg/dL). The maximum dose acceptable is 300 mL for diagnostic coronary arteriography.

(B) Laskey’s formula [99]: volume of contrast to calculated creatinine clearance ratio with a cut-off point of the ratio at 3.7 or, better, at 2.0: below a ratio of 2.0 CIN would be a rare complication, but would increase dramatically at a ratio of 3.0 [97, 100].

(C) Ratio of grams of iodine to the calculated creatinine clearance; a ratio of 1.42, or even better a ratio of 1.0, would prevent CIN [97].

The fifth measure is to ensure an adequate hydration of the patient [101,102]. The old practice to limit fluid intake starting the day before IRCA administration must be abolished. Instead, we have to give volume supplementation: e.g. 500 mL of water orally before and 2,500 mL for 24 hours after contrast administration in order to secure urine output of at least 1 mL/min in a non-dehydrated patient [103]. In high-risk patients it is suggested an i.v. infusion of 0.9% saline at a rate of approximately 1 mL/kg b.w. per hour, beginning 6–12 hours before the procedure and continuing for up to 12–24 hours after the radiographic examination, if urine output is appropriate and cardiovascular condition allows it [16, 101]. Hydration, in fact, causes expansion of intravascular volume, suppression of renin-angiotensin system and consequent reduction of renal vasoconstriction and hypoperfusion. Furthermore, the increased diuresis will limit the duration of IRCA contact with renal tubu-
lar walls and consequently the toxicity on tubular epithelium [104,105].

On the basis of clinical studies and meta-analysis some Authors prefer sodium bicarbonate hydration to sodium chloride [106-114]. This because urinary excretion of bicarbonate decreases the acidification of urine, thereby reducing the production and increasing the neutralization of oxygen free radicals; this will protect the kidney from injury by contrast agents [109,110,115,116]. The dosage suggested for an emergency coronary angiography or intervention is: 154-mEq/L infusion of sodium bicarbonate as a bolus of 3 mL/kg b.w./hour for 1 hour before the administration of contrast agent, followed by 1 mL/kg/hour for 6 hours during and after the procedure [107]. The ERBP "recommends volume expansion with either isotonic sodium chloride or sodium bicarbonate solutions, rather than no volume expansion, in patients at increased risk for CIN" [95].

The sixth measure is the use of drugs protecting the kidneys. We have mentioned that ROS have been proven to play an important role in the renal damage caused by IRCA. Hence, antioxidants represent the main type of drugs that has been shown to reduce the incidence of CIN. The antioxidant N-acetylcysteine [117] is believed to act either as a free-radical scavenger or as a reactive sulphydryl compound as well as a factor able to increase the vasodilating effect of NO [16,33,118]. Pretreatment with NAC has been demonstrated to reduce IRCA-induced cytotoxicity in human embryonic kidney cells treated with ioxitalamate, iopromide and ioxidanol [119] and to ameliorate the ischemic ARF in animal models [120]. Its use in humans has given controversial results [8,121-129]. We may give NAC to high-risk patients either as an oral dose of 600 mg twice daily the day before and the day of procedure [16] or, in patients unable to take the drug orally, with an i.v. dose of 150 mg/kg over half an hour before the procedure or 50 mg/kg administered over 4 hours [37,94,122].

Conflicting results have been obtained with another antioxidant, ascorbic acid [119,130-132] at a dosage of 3 g orally 2 hours before the procedure and 2 g during the night and in the morning after the procedure. In a recent meta-analysis, with 1536 patients who completed the trial, patients receiving ascorbic acid had a 33% reduced risk of developing CIN [133]. Tasanarong et al [134] have used α-tocopherol and γ-tocopherol as antioxidants to prevent CIN: the oral administration of either 350 mg/day of α-tocopherol or 300 mg/day of γ-tocopherol 5 days prior to the coronary procedure and continued for a further 2 days post-procedure, in combination with 0.9% saline (1 mL/kg/h for 12 hours before and 12 hours after) was demonstrated to be effective in protecting against CIN in patients with CRF undergoing coronary procedures with iopromide: CIN developed in 14.9% of cases in the placebo group, but only in 4.9% and 5.9% in the α- and γ-tocopherol groups, respectively [134].

Nebivolol, a third-generation β1-adrenergic receptor antagonist, has been suggested for protecting the kidney against CIN because of its antioxidant and NO-mediated vasodilating action [135,136]: at a dosage of 5 mg/day for one week or 5 mg every 24 hours for 4 days, it decreased the incidence of CIN in patients with renal dysfunction undergoing coronary angiography [137,138].

Several studies have demonstrated the protective effect of statins against the CIN [139-145] because of their antioxidant, anti-inflammatory, and antithrombotic properties and their vasodilator activity mediated by NO, which improves renal microcirculation [146,147]. Rosuvastatin has been shown to be nephroprotective at a dosage of 10 mg/day for five days, two days before, three days post the radiographic procedure, in diabetic patients with CRF undergoing coronary/peripheral arterial angiography [139], and at a dosage of 40 mg on admission followed by 20 mg/day in patients with acute coronary syndrome [140]. Atorvastatin (40 mg/day) 3 days before the procedure or 80 mg 12 hours before intervention with another 40-mg pre-procedure, followed by long-term treatment of 40 mg/day) had a protective effect on renal function preventing CIN and shortening hospital stay [148,149].

The outer renal medulla, under normal physiological conditions, receives little oxygen (O₂) because of its distance from the descending vasa recta, despite its high local O₂ consumption [30,150,151]. Thus, it has been suggested to use furosemide to decrease the reabsorption in the thick ascending limb of the Henle’s loops that are here located. IRCA induce also an osmotic diuresis that will increase fluid delivery and consequently tubular reabsorption in the ascending limb of Henle’s loops, thereby increasing both energy need and O₂ consumption: the result will be a worsening of renal medullary hypoxia [30,150,151]. The treatment for CIN during coronary angiography should include a combination of hydration plus furosemide; this procedure has been called ‘Renal Guard’ by Guastoni et al [156]: the result was a significantly lower incidence of CIN when this procedure was compared to the patients treated with hydration only.

Under physiological conditions, the Na’/Ca²⁺ exchanger (NCX), pumps Ca²⁺ out of the renal tubular epithelial cells using the Na’ concentration gradient across the cell membrane to keep
the intracellular Ca\(^{2+}\) levels low. In pathological conditions, such as CIN, NCX can reversely extrude Na\(^{+}\) for Ca\(^{2+}\) influx, resulting in intracellular Ca\(^{2+}\) overload that is believed to be a key factor in ischemic cell injury in CIN [37,157]. Thus, calcium channel blockers have been hypothesized to have protective effects against CIN. However, their use has given controversial results, protective for some Authors [158,159], non-protective according to others [160-162].

Very recently, Pequero et al [163] have suggested to use Nitrates to reduce the incidence of CIN. In a retrospective, single-center study these Authors investigated whether the use of nitrate in 199 patients undergoing percutaneous coronary artery intervention could reduce the incidence of CIN. Post-procedure renal function was compared between 112 patients who received nitrates prior to coronary intervention and 87 who did not. Multivariate logistic regression analysis demonstrated that nitrate use was independently correlated with a reduction in the development of CIN (OR = 0.33.9, 95% CI 0.157-0.709, p = 0.004). Additionally, amongst various methods of nitrate administration, intravenous infusion was shown to be the most efficacious route in preventing renal impairment (OR = 0.42, 95% CI 0.20-0.90, p = 0.03). According to these data, the use of nitrates prior to PCI, particularly as intravenous nitroglycerin infusion, may be associated with a decreased incidence of CIN.

#### Treatment by dialysis

Treatment by haemodialysis or haemofiltration immediately after the radiographic procedure has been suggested with the purpose to remove IRCA. Schindler et al [164] demonstrated, in patients with CRF (the great majority in chronic dialysis), that different dialysis techniques remove IRCA, and that high-flux haemodialysis and haemodiafiltration remove IRCA more effectively than low-flux haemodialysis and haemofiltration. But Lehnert et al [165] demonstrated that, even though haemodialysis eliminates IRCA, it does not prevent the occurrence of CIN. Vogt et al [166] performed a randomized trial to test whether CIN can be avoided by prophylactic haemodialysis immediately after the administration of low-osmolality IRCA in patients with CRF (baseline serum creatinine level >2.3 mg/dL); renal function was recorded before and during the 6 days after administration of contrast media. Hemodialysis did not diminish the rate of CIN. These studies suggest that, even when dialysis is performed immediately, the early damage has already occurred and cannot be reversed [167]. Hence, the effects of haemodialysis have been negative [168].

There are, however, a few exceptions. Lee et al [169] have compared intravenous isotonic saline and prophylactic haemodialysis in 82 patients with CRF referred for coronary angiography; they randomly received either normal saline intravenously and prophylactic haemodialysis (dialysis group, n = 42) or fluid supplement only (control group, n = 40). Prophylactic haemodialysis lessened the reduction in creatinine clearance within 72 hours (<0.001). Temporary renal replacement therapy was required in 35% of the control patients and in 2% of the dialysis group; five of the controls and none of the dialysis patients required long-term dialysis after discharge (p=0.018). For the patients not requiring chronic dialysis, 13 in the control group (37%) and 2 in the dialysis group (5%) had an increase in SCr at discharge of more than 1 mg/dL from baseline (p < 0.001). The Authors concluded that the prophylactic haemodialysis is effective in improving renal outcome in CRF patients undergoing coronary angiography.

Marenzi et al [170] have demonstrated that hemofiltration is an effective strategy for preventing CIN in patients with CRF undergoing cardiovascular procedures provided that is performed for 6 hours before and for 18 to 24 hours after contrast exposure.

Better results have been obtained with continuous venovenous hemofiltration (CVVH). Thus, La Manna et al [171] have proposed the CVVH technique in preventing CIN in high-risk patients undergoing interventional cardiovascular procedures involving the administration of IRCA. CVVH in 12 patients with severe chronic renal impairment and at least two severe co-morbidities significantly improved eGFR and SCr after the use of iodixanol. Renal function, in fact, evaluated as SCr and as e-GFR, did not worsen but was improved when the patients left hospital 7 days after the radiological procedure, being significantly better than that on hospital admission. More recently, Guastoni et al [172] performed CVVH in 53 consecutive patients with eGFR <30 mL/min/1.73 m² undergoing diagnostic or interventional coronary procedures using iopamidol; CVVH was started immediately after the angiographic procedure. Six-hour CVVH resulted in iopamidol removal comparable with that of 12-hour diuresis (i.e. 43% vs 42%). CIN occurred in only 7.5% of patients of the total population investigated.

#### Table - Iodinated Contrast Media Commonly Used in Clinical Practice

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Iodine content (mg/mL)</th>
<th>Osmolality (mOsm/kg)</th>
<th>Osmolality Viscosity (type)</th>
<th>Osmolality at 21°C (cps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diatrizoate (Hypaque 50)</td>
<td>Monomer</td>
<td>300</td>
<td>1.550</td>
<td>HOCM</td>
<td>10.5</td>
</tr>
<tr>
<td>Metrizoate isopaque (Contrav 370)</td>
<td>Monomer</td>
<td>370</td>
<td>2.100</td>
<td>HOCM</td>
<td>5.4</td>
</tr>
<tr>
<td>Ioxaglate (Hexabrix)</td>
<td>Dimer</td>
<td>320</td>
<td>580</td>
<td>LOCM</td>
<td>7.5</td>
</tr>
<tr>
<td>Nonionic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iopamidol (Isovist-370)</td>
<td>Monomer</td>
<td>370</td>
<td>796</td>
<td>LOCM</td>
<td>9.4</td>
</tr>
<tr>
<td>Iohexol (Omnipaque 350)</td>
<td>Monomer</td>
<td>350</td>
<td>884</td>
<td>LOCM</td>
<td>10.4</td>
</tr>
<tr>
<td>Iodixanol (Visipaque 320)</td>
<td>Dimer</td>
<td>320</td>
<td>290</td>
<td>IOCM</td>
<td>11.8</td>
</tr>
</tbody>
</table>

The osmolality of contrast media is compared with the osmolality of plasma. HOCM = High Osmotic Contrast Media have the highest osmolality, i.e. 5-8 times the osmolality of plasma. LOCM = Low Osmotic Contrast Media have an osmolality still
higher than plasma, i.e. 2–3 times the osmolality of plasma. IOCM = Iso Osmotic Contrast Media have the same osmolality as plasma. Cps: Viscosity in Centipoise.

(Reproduced from [4] with permission.)

Data of viscosity from [173].

Conflicts of Interest

All Authors have no potential conflicts of interest to disclose.

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