How to Prevent Contrast-Induced Nephropathy in Clinical Practice

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Abstract

After the description of the Contrast-Induced Nephropathy (CIN), its epidemiology and its pathogenesis, the risk factors for the development of CIN are discussed in depth, the main ones being pre-existing renal impairment, particularly 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 the main rules in prevention: monitoring renal function, discontinuation of potentially nephrotoxic drugs, use of either iodixanol, an iso-osmolar contrast medium or iopamidol, a low-osmolar contrast medium at the lowest dosage possible. The main procedure for prevention of CIN is an adequate hydration of the patient with either isotonic sodium chloride or sodium bicarbonate solutions. The antioxidant N-acetylcysteine may be added orally or intravenously. Other antioxidants, such as vitamin C (ascorbic acid) and vitamin E (α- or γ-tocopherol), compounds with antioxidant properties (e.g. Mesna), and β1-adrenergic receptor antagonists (e.g. Nebivolol) require further studies before deciding their use in clinical practice to prevent CIN.

ABBREVIATIONS

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; LOCM: Low-Osmolar Contrast Media; NO: Nitric Oxide; ROS: Reactive Oxygen Species; SOD: Superoxide Dismutase; MBL: Mannose-Binding Lectin; HOCM: High-Osmolar Contrast Media; IOMC: Iso-Osmolar Contrast Media; Mesna: Mercapto-Ethane-Sulfonate Na; MASP-2: Mbl-Associated Serine Proteases-2; MRI: Magnetic Resonance Imaging

CONTRAST-INDUCED NEPHROPATHY (CIN)

Contrast-Induced Nephropathy (CIN); other definition: Contrast-Induced Acute Kidney Injury - CI-AKI) is an iatrogenic disease that may occur when radiographic contrast media are injected intravenously or intra-arterially to improve the visibility of internal organs and structures in X-ray based imaging techniques, such as radiography and Computed Tomography (CT), or for percutaneous coronary intervention using contrast agents. It may be so defined in any case of acute renal failure occurring (especially in patients with pre-existing renal impairment and in those with diabetes) [1] within 48-72 hrs of exposure to intravascular radiographic contrast agents that cannot be attributed to other causes. It is usually a nonoliguric acute renal failure with asymptomatic transient decline in renal function, occurring generally within 48-72 hrs of contrast administration, peaking on the third to fifth day, and returning to baseline within 10–14 days [2]. It is mirrored by an absolute (0.5 mg/dl or greater) or relative (by 25% or greater) increase in serum creatinine from baseline [3,4] or, better, by a decrease (to 30-60 mL/min · creatinine clearance – or less) in the estimated glomerular filtration rate (eGFR), i.e. the creatinine clearance calculated using the MDRD (Modification of Diet in Renal Disease) calculation [5] or the very simple Cockcroft-Gault formula [6]. The risk for CIN in outpatients with an eGFR greater than 45 mL/min per 1.73 m² seems to be extremely low, estimated to be in the region of about 2% [7].

In 10% of patients with pre-existing renal failure undergoing coronary angiography [8] and in ≤1% of all patients undergoing percutaneous coronary intervention using contrast agents [9] CIN may cause a severe acute renal failure with oliguria (<400 mL/24 hrs) requiring dialysis, which is accompanied by a high mortality rate. The management of CIN is the same as that for acute renal failure due to other causes [10-12].

In order to determine the effect of Intravenous (IV) Low-Osmolar Contrast Media (LOCM) on the development of post-CT CIN, Davenport et al [13] performed a retrospective study. In 20,242 adult in patients undergoing CT examinations over a period of 10 years (10,121 untreated and 10,121 treated with IV contrast media, stratified
by pre-CT stable eGFR) observed that IV LOCM is a risk factor for nephrotoxicity in patients with a stable eGFR <30 mL/min/1.73 m²; there is a trend toward significance at 30-44 mL/min/1.73 m²; it does not appear to be a nephrotoxic risk factor in patients with a pre-CT eGFR >45 mL/min/1.73 m² [13,14].

In another recent retrospective study involving 53,439 patients in whom serum creatinine (ranging between <1,5 and ≥2 mg/dL) was regularly checked to determine the effect of IV iodinated contrast material exposure to the incidence of CIN, McDonald et al [15] found that the incidence of CIN was not significantly different between the contrast group and control group. Thus, they suggest that intravenous iodinated contrast agents are not the cause of decreased renal function after contrast material administration.

In a systematic review and meta-analysis of controlled studies the same authors [16] examined the incidence of CIN in patients exposed to IV contrast medium compared with patients without contrast (control group); they demonstrated a similar incidence of CIN, dialysis, and death between the contrast group and control group [16].

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 [4]. This is mainly related to (a) the intra-arterial injection, (b) the high dosage of the contrast used and (c) 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 and diabetes [7].

The relationship of CIN to long-term adverse events (e.g. death, stroke, myocardial infarction, end-stage kidney disease, percutaneous coronary revascularization, coronary artery bypass graft surgery, cardiac arrest, etc) has been studied in 294 patients, with follow-up of at least 1 year after contrast exposure. The rate of long-term adverse events was higher in individuals with CIN [17].

Pathogenesis

The mechanisms of nephrotoxicity by contrast agents are not fully understood [18]. It can be reasonably assumed that CIN is due to many factors, including an initial increase followed by a more prolonged decrease in renal blood flow, a decrease in glomerular filtration rate, a decrease in Nitric Oxide (NO) and a severe reduction in medullary blood flow with renal ischaemia, hypoxia and direct tubular damage, formation of Reactive Oxygen Species (ROS) [19-23], increased intratubular pressure secondary to contrast-induced diuresis, increased urinary viscosity and tubular obstruction, all frequently associated with dehydration and a decrease in the effective intravascular volume [2,10,24]. In vivo experiments in rats have demonstrated that the decrease in cortical and medullary microvascular blood flow induced by contrast media is partly accounted for by the downregulation of endogenous renal cortical and medullary NO synthesis [25]. To support the role of ROS generated in contrast media-induced vasoconstriction, the use of the Superoxide Dismutase (SOD) mimetic Tempol reduced iodixanol-induced vasoconstriction [26]. More recent work using a recombinant manganese SOD administered in vivo to rats undergoing diatrizoate treatment caused an improvement in GFR and a reduction in renal histologic damage [27].

Direct toxicity on tubular epithelial cells by contrast agents has been observed in studies of isolated tubule segments and cultured cells causing disruption of cell integrity, generation of ROS and apoptosis. Contrast agents cause cellular damage to endothelial cells, i.e. the first cells to come in contact with intravenously-injected contrast agents [2]. The contrast agents are then filtered by glomeruli and become concentrated within the tubules, thereby exposing the tubular cells to an even worse direct damage [28]. In vitro cell culture studies have shown that all types of contrast agents cause a decrease in cell viability [29-33]. The biochemical changes underlying these effects have been extended to studying changes in major intracellular signalling pathways involved in cell survival, death and inflammation [31-36]. In vivo studies in cultured renal tubular cells [37-39]. Contrast media can cause perturbation of mitochondrial enzyme activity and apoptosis [40]. Studies in animals as well as in vitro studies suggest, in fact, that they can directly induce caspase-mediated apoptosis of renal tubular cells [41-46].

Some studies have demonstrated the crucial role played by mannose-binding lectin (MBL, a protein of the lectin pathway of the complement system) in aggravating the inflammatory response and the tissue damage during ischemia/reperfusion injury of several organs, including the kidney [47,48], that is alleviated by inhibition with C1 inhibitor, a potent MBL and lectin pathway inhibitor [49]. In experimental ischemia/reperfusion models, MBL has been found to induce tubular cell death, independent of the complement system, and contribute to endothelial dysfunction, after binding to vascular endothelial cells, by triggering a pro-inflammatory reaction [50-52]. Urinary MBL is increased after administration of contrast agents and in humans with CIN, suggesting some role of MBL in causing CIN [49,53]. In a trial assessing the importance of serum MBL for the development of CIN, the deficiency of this lectin did not influence the occurrence of CIN as defined by a serum creatinine increment; but it was associated with an increase in cystatin C after the administration of a contrast agent [54]. We have to consider that the increase of serum creatinine after contrast media is delayed, usually achieving a maximum two to five days after contrast exposure. Serum cystatin C, instead, is a more sensitive marker and has been shown to increase earlier, to peak 24 hours after contrast administration, thereby detecting even subtle changes in eGFR after acute kidney injury including CIN [55-58]. Thus, in this clinical trial, subjects with MBL deficiency were almost two-times less likely to develop an increase of ≥10% in cystatin C after administration of the contrast agent. This suggests that deficiency of MBL might attenuate some of the detrimental effects of contrast media [54].

Identification of patients at high risk for the development of CIN

The European Society of Urogenital Radiology has suggested that the real risks for CIN are represented by pre-existing renal impairment, particularly secondary to diabetic nephropathy, salt depletion and dehydration, congestive heart failure, an age greater than 70 years and concurrent use of nephrotoxic drugs [3,59].

Undoubtedly, pre-existing impairment of renal function, irrespective of cause, represents the main risk factor for CIN. 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 [2]. The incidence of CIN in patients with chronic renal failure ranges from 14.8 to 55% [4]. Diabetes
Central is believed to be low and correlated with β2-microglobulin levels, in patients with multiple myeloma with a normal serum creatinine [10,22,79-78].

To congestive heart failure, liver cirrhosis, or salt depletion secondary to severe dehydration, reduction of effective intravascular volume due to the coupling of chronic kidney disease and diabetes, particularly if the arterial injection is suprarenal [1, 90-96]. The second rule is that potentially nephrotoxic drugs should be discontinued before contrast administration [2].

The role of renin-angiotensin-aldosterone system blocking agents (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) in the pathophysiology of CIN is still controversial [66]. Many authors believe that these drugs should be discontinued in patients with chronic renal disease at high risk for developing CIN [67-73]. Others deny a negative influence in the incidence of CIN in stable patients with chronic renal failure [74]. KDIGO does not deem it necessary to discontinue these medications prior to contrast administration [75]. Other risk factors include: prolonged hypotension might be the result of this side effect explaining the beneficial effects of prophylactic hydration in preventing CIN [97].

It has been shown that the use of LOCM rather than HOCM is beneficial in preventing CIN in patients with pre-existing renal failure [98-101]. However, other studies comparing HOCM and LOCM have shown a much less than anticipated advantage for the ability of LOCM to decrease the risk of CIN, even in subjects with pre-existing renal impairment [93,97,100]. Recent studies and meta-analyses have found no significant difference in the rates of CIN between IOCM and LOCM [102-105]; only that the LOCM iohexol seems to be more nephrotoxic [98,106].

Table 1: Iodinated Contrast Media Commonly Used in Clinical Practice.

<table>
<thead>
<tr>
<th>Name</th>
<th>mOsM/kg</th>
<th>Osmolality type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metrizoate Isopaque (Conray 370)</td>
<td>2,100</td>
<td>HOCM</td>
</tr>
<tr>
<td>Diatrizoate (Hypaque 50)</td>
<td>1,550</td>
<td>HOCM</td>
</tr>
<tr>
<td>Ioxaglate (Hexabrix)</td>
<td>580</td>
<td>LOCM</td>
</tr>
<tr>
<td>Iopamidol (Isovue-370)</td>
<td>796</td>
<td>LOCM</td>
</tr>
<tr>
<td>Iohexol (Omnipaque 350)</td>
<td>884</td>
<td>LOCM</td>
</tr>
<tr>
<td>Iodixanol (Visipaque 320)</td>
<td>290</td>
<td>LOCM</td>
</tr>
<tr>
<td>Iodixanol (Visipaque 320)</td>
<td>290</td>
<td>LOCM</td>
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</table>

Osmolality of contrast media compared with the osmolality of plasma. HOCM: High-Osmolar Contrast Media, the highest osmolality, 5–8 times the osmolality of plasma. LOCM: Low-Osmolar Contrast Media, an osmolality 2–3 times the osmolality of plasma. IOCM: Iso-Osmolar Contrast Media, the same osmolality as plasma.

a dehydrating effect, particularly when high doses are given as during cardiac catheterization procedures. Thus, the high incidence of CIN might be the result of this side effect explaining the beneficial effects of prophylactic hydration in preventing CIN [97].

It has been shown that the use of LOCM rather than HOCM is beneficial in preventing CIN in patients with pre-existing renal failure [98-101]. However, other studies comparing HOCM and LOCM have shown a much less than anticipated advantage for the ability of LOCM to decrease the risk of CIN, even in subjects with pre-existing renal impairment [93,97,100]. Recent studies and meta-analyses have found no significant difference in the rates of CIN between IOCM and LOCM [102-105]; only that the LOCM iohexol seems to be more nephrotoxic [98,106].

MEASURES TO PREVENT CIN

Main rules in prevention of CIN

The first general rule of prevention is that in any patient undergoing any radiographic procedure, renal function should be monitored by measuring serum creatinine and calculating the eGFR. This is even more important in patients at high risk of CIN, in whom serum creatinine and eGFR should be checked before and once daily for 5 days after the radiographic procedure [10].

The second rule is that potentially nephrotoxic drugs should be discontinued before the contrast procedure. We refer to aminoglycosides, vancomycin, amphotericin B, metformin and nonsteroidal anti-inflammatory drugs [2]. Sometimes aminoglycosides are necessary and cannot be discontinued. For these conditions the European Renal Best Practice position [107] is “not using more than one shot of aminoglycosides for the treatment of infections... in patients with normal kidney function in steady state, aminoglycosides are administered as a single-dose daily rather than multiple-dose... monitoring aminoglycoside drug levels”. For amphotericin B, the ERBP recommends that saline loading be implemented in all patients receiving any formulation of amphotericin B [107]. The potential harm by metformin (an oral antihyperglycemic medication, used to treat type II diabetes, that stimulates intestinal production of lactic acid) is the severe lactic acidosis that may follow the occurrence of renal failure (since metformin is excreted unchanged almost entirely by the kidneys, it is retained in case of CIN); this lactic acidosis can be fatal. Thus, the drug has to be discontinued at least 12 hours before the contrast and not be resumed for a minimum of 36 hours after...
the procedure, or longer if the serum creatinine has not returned to
baseline [108].

The third rule is the choice of the least nephrotoxic radiopaque
agent. LOCM (e.g. iohexol) are less nephrotoxic than HOCM (e.g.
diatrizoate). Moreover, IOCM (e.g. iohexol) seem to be less
nephrotoxic than LOCM [10]. In a multicenter, randomized, double-
blind comparison of iopamidol (LOCM) and iodixanol (IOCM),
performed in patients with chronic kidney disease, the rate of CIN
was not statistically different after the intraarterial administration
of iopamidol or iodixanol to high-risk patients, with or without diabetes
mellitus [103]. Thus, iodixanol (IOCM) and iopamidol (LOCM)
appear to be contrast agents of choice to reduce risk of CIN.

The fourth rule is to use the lowest dosage possible of contrast
corona. High doses of contrast agents are required in percutaneous
coronary intervention. For this procedure, some formulas have been
suggested to calculate the dosage that is least dangerous for renal
function:

(A) Cigarroa’s formula: 5 mL of contrast per kg b.w./Serum
Creatinine (mg/dL) with maximum dose acceptable of 300 mL for
diagnostic coronary arteriography [109].

(B) Laskey’s formula: volume of contrast to calculated creatinine
clearance ratio with a cut-off point of the ratio at 3.7 for percutaneous
coronary intervention; a ratio >3.7 would be associated, following
contrast use, with a decrease in creatinine clearance [110]; recently
the cut-off point has been placed at 2.0: below a ratio of 2.0 CIN
would be a rare complication of percutaneous coronary intervention,
but it would increase dramatically at a ratio of 3.0 [111,112].

(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 [111].

Adequate hydration

The main procedure for prevention of CIN is an adequate
hydration of the patient [113,114]. The old suggestion to limit fluid
intake starting the day before contrast administration must be
abolished and replaced by volume supplementation: e.g. 500 mL of
water or soft drinks (e.g. tea) 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 [115]. In high-risk patients
adequate hydration may be obtained by IV 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; this may be done only if urine
output is appropriate and cardiovascular condition allows it [10,113].
The rationale for volume supplementation is that hydration causes
expansion of intravascular volume, suppression of renin-angiotensin
cascade and consequent reduction of renal vasoconstriction
and hypoperfusion. The resulting increase of diuresis will limit
the duration of contrast material contact with renal tubules and
consequently its toxicity on tubular epithelium [116,117].

Some clinical studies and meta-analysis have shown that sodium
bicarbonate hydration is superior to sodium chloride [118-126] at
least when using LOCM [127]. For patients undergoing an emergency
coronary angiography or intervention the following protocol has
been used: 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,
followed by 1 mL/kg/hour for 6 hours during and after the procedure
[119]. The rationale for using bicarbonate infusion is explained in
that any condition (such as acetazolamide administration or sodium
bicarbonate infusion) that increases bicarbonate excretion decreases
the acidification of urine and renal medulla. Consequently, this will
reduce the production and increase the neutralization of oxygen free
radicals, thereby protecting the kidney from injury by contrast agents
[121,122,128,129].

Other investigators did not find a benefit with sodium bicarbonate
hydration versus sodium chloride [130-133]. Some authors found even an increased incidence of CIN with the use of
intravenous sodium bicarbonate [134]. 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” [107].

Antioxidants

Since ROS have been proved to play an important role in the renal
damage caused by iodinated radiographic agents, the antioxidant
N-acetylcysteine has been thought to act either as a free-radical
scavenger or as a reactive sulphhydryl compound as well as a factor
able to increase the vasodilating effect of NO [10,21,135]. Short-
duration pretreatment with N-acetylcysteine has been demonstrated
to reduce contrast-induced cytotoxicity in human embryonic kidney
cells treated with the ionic HOCl ioxithalamate, non-ionic LOCM
iopromide and the IOMC ioxidanol [136] and to ameliorate the
ischemic renal failure in animal models [137]. Despite controversial
results observed in high risk patients [134,138-147], it has been
suggested to use N-acetylcysteine in high-risk patients either with
an oral dose of 600 mg twice daily the day before and the day of
procedure [10] or, in patients unable to take the drug orally, with an
IV dose of 150 mg/kg over half an hour before the procedure or 50
mg/kg administered over 4 hours [139].

Other antioxidants have been suggested for use against CIN:
vitamin C (ascorbic acid), vitamin E (α- or γ-tocopherol) and Mesna.

Conflicting results have been obtained with the use of ascorbic
acid [136,148-150] 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 [148,149]. N-acetylcysteine (1,200 mg orally twice a day
before and on the day of coronary catheterization) has been shown to
be more beneficial in preventing CIN than ascorbic acid, particularly
in diabetic patients with renal insufficiency undergoing coronary
angiography [151]. In a recent meta-analysis, with 1536 patients who
completed the trial, patients receiving ascorbic acid had a 33% less
risk of developing CIN [152].

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)
has been demonstrated to be effective in protecting against CIN in
patients with chronic kidney disease undergoing coronary procedures
with Iopromide (LOCM): 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 [153].

Mesna (mercaptopo-ethane-sulfonate Na) is an agent with
antioxidant properties that has been shown to reduce free radicals and
restore reduced glutathione levels after ischemic renal failure [154].
In a randomized controlled trial using Mesna for the prevention of CIN, the IV administration of 1600 mg Mesna versus placebo, together with intravenous hydration with 0.9% saline, resulted in the occurrence of CIN in 7 patients in the placebo group and none in the Mesna group [155]. Further studies would be necessary to confirm such a positive outcome.

**Nebivolol**

Nebivolol, a third-generation β1-adrenergic receptor antagonist [156,157], has been hypothesized to protect the kidney against CIN through its antioxidant and NO-mediated vasodilating action [158]. In experimental rats it has been shown to decrease medullary congestion, protein casts and tubular necrosis, systemic and renal oxidative stress, microproteinuria secondary to contrast media, and to increase the kidney nitrite level decreased by contrast media [158]. Nebivolol (5 mg/day for one week or 5 mg every 24 hours for 4 days) decreased the incidence of CIN in patients with renal dysfunction undergoing coronary angiography [159,160].

**Statins**

Recent studies have shown a beneficial effect of statins to prevent CIN in patients undergoing percutaneous coronary intervention [161-166]. This is not surprising, considering that hypercholesterolemia has been suggested to be a predisposing factor to CIN on the basis of a study in experimental CIN, characterized by compromised NO synthesis and enhanced ROS generation [167]. But the nephroprotective effect of statins has been attributed to their antioxidant, anti-inflammatory, and antithrombotic properties and to their vasodilator property mediated by NO, that improves renal microcirculation [168,169]. Rosuvastatin (10 mg/day for five days, two days before, three days post the procedure) reduced the risk of CIN in patients with diabetes mellitus and chronic kidney disease undergoing coronary/peripheral arterial angiography [170]. Also simvastatin had a dose-dependent nephroprotective effect in experimental rats treated with radiocontrast agents [168]. Patients on pravastatin had an even lower incidence of CIN than patients on simvastatin [171,172]. Short-term atorvastatin (40 mg/day 3 days before the procedure) and chronic atorvastatin therapy had a protective effect on renal function after coronary angiography [173]. Patients undergoing percutaneous coronary intervention were given short-term pretreatment with atorvastatin (80 mg 12 hours before intervention with another 40-mg pre-procedure, followed by long-term treatment of 40 mg/day); this prevented CIN and shortened hospital stay [174].

**Steroids**

It has been recently suggested that high-dose steroids (1 mg/kg of oral prednisone, 12-24 hours before and 24 hours after the angiographic procedure) given concurrently with IV saline (1 ml/kg/hour of 0.9% saline, 12 hours before the procedure) may protect renal tubules against either iodixanol or iohexol [175]. This is based on the fact that steroids may have a favorable impact on inflammation and on renal tubular cell apoptosis and necrosis, as observed in models of renal ischemia-reperfusion in which dexamethasone had a protective effect against injury [176].

**Diuretics and Anp**

Since enhanced transport activity with oxygen consumption is a principal cause of renal hypoxia and both furosemide and mannitol reduce transport activity, it has been suggested to use furosemide or mannitol (associated with saline infusion to prevent salt depletion) to protect against CIN. Several studies, however, have demonstrated either no effect in protecting against contrast media or even deleterious effect of furosemide and mannitol on renal function [177-179]. Thus, diuretics should be avoided before contrast exposure in high-risk patients who are susceptible to volume depletion [67].

Use of Atrial Natriuretic Peptide (ANP) has also failed to protect against CIN [179,180].

**CALCIUM CHANNEL BLOCKERS**

Calcium Channel Blockers have been hypothesized to have protective effects against CIN. The rationale is the following: Ca²⁺ overload is considered to be a key factor in CIN; the increase in intracellular calcium provokes a vasoconstrictive response in intrarenal circulation and would be an important mediator of epithelial cell apoptosis and necrosis. The Na⁺/Ca²⁺ exchanger system is one of the main pathways of intracellular Ca²⁺ overload. It has been demonstrated that in rats the pretreatment with KB-R7943, an inhibitor of the Na⁺/Ca²⁺ exchanger system, significantly and dose-dependently suppresses the increase of serum creatinine following diatrizoate administration [181]. Hence, the use of Calcium Channel Blockers has been suggested for prevention of CIN, but their use has given controversial results, sometimes protective [182,183] and sometimes with no benefit at all [177,184-186].

**Other substances**

Urinary adenosine is increased after contrast medium administration: thus, it has been thought that Adenosine Antagonists (theophylline, aminophylline) could have protective effects against contrast media; but their use has given controversial results. Some authors have observed beneficial effects against CIN [187-190], others have denied any beneficial results [191,192].

Dopamine and Dopamine Agonists (e.g. fenoldopam, a selective dopamine-1 receptor agonist with vasodilatory properties) have given controversial results in protecting against CIN, some positive [193-195], others negative [142,179,192,193,196,197]. On the basis of our present knowledge, it is better to avoid them, considering their adverse effects (arrhythmia with dopamine, and systemic hypotension with intravenous fenoldopam).

The plasma and urine levels of endothelin-1 are increased in diabetes and after exposure to high doses of contrast media; this has suggested a role of endothelin-1 in diabetic nephropathy and in CIN [22,198,199]. However, endothelin Receptor Blockers have been proven deleterious as a prophylactic tool against CIN [200].

Prostaglandin E1 has given some positive protective results on renal function following contrast medium injection in patients with preexisting renal impairment [201], whilst L-arginine has shown no benefit or even harm [202].

There are some experimental substances that seem promising in preventing CIN, but require further evaluation. Thus, sodium butyrate has been shown to decrease the activation of Nuclear Factor kappa B (NF-κB), thereby reducing inflammation and oxidative damage in the kidney of rats subjected to CIN [203]. Similarly, the human serum albumin–Thioredoxin (HSA–Trx) has been demonstrated to prevent CIN and renal tubular apoptosis, via its extended antioxidative action.
in a rat model of ioversol-induced CIN [204]. Thioredoxin-1 – Trx - is a ubiquitous low-molecular-weight protein, produced in the human body in response to oxidative stress conditions. Finally, as already mentioned, an important role in CIN may be played by mannose-binding lectin (MBL), with observations that MBL and MASP-2 (MBL-associated serine proteases-2) were significantly upregulated in the urine samples taken 12-18 hours after administration of contrast media compared to the pre-procedural urine sample [53]. Treatment with anti-MBL monoclonal antibodies or inhibitors of MASP might be protective against contrast media in order to prevent CIN [49].

Haemodialysis or haemofiltration

It has been suggested to remove radiocontrast media by haemodialysis or haemofiltration immediately after the radiographic procedure. However, the extracorporeal removal of contrast agents did not decrease the incidence of acute renal failure in high-risk patients [205-208]. The ERBP does “not recommend using prophylactic intermittent haemodialysis or haemofiltration for the risk patients” [205-208]. The ERBP does “not recommend using prophylactic intermittent haemodialysis or haemofiltration for the purpose of prevention of CIN” [107].

Alternative imaging method

KDIGO guidelines for Acute Kidney Injury Work Group has stated that we should “consider alternative imaging methods in patients at increased risk for CI-AKI” [75]. In fact, Magnetic Resonance Imaging (MRI) with Gadolinium-Based Contrast Agents may be an alternative imaging method. Gadolinium-Based Contrast Agents are not iodinated compounds; thus, there is no risk for CIN [209]. However, the use of Gadolinium-Based Contrast Agents may be associated with acute renal failure or nephrogenic systemic fibrosis, i.e. a rare pathology that causes fibrosis of the skin and connective tissues throughout the body involving several organs, kidney included; this occurs particularly in patients with pre-existing renal failure [210,211].

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