Facts and fallacies concerning the prevention of contrast medium–induced nephropathy

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Identify risk factors for contrast medium-induced nephropathy (CMIN).
2. Describe effective prophylaxis for CMIN.
3. Use this information in a clinical setting.

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Objective: **The aim of this article is to extract from recent medical literature and nephrologic practice the facts and fallacies concerning the possible prophylaxis of contrast medium–induced nephropathy.**

Data Sources, Study Selection, and Data Extraction: **A MEDLINE/PubMed search (1985 to January 2006) was conducted, including all relevant articles investigating the pathogenesis and prevention of contrast medium–induced nephropathy from a nephrologic critical point of view.**

Data Synthesis: **Considerable efforts have been made to develop pharmacologic therapy for the prevention of contrast medium–induced nephropathy, especially in patients at risk, such as elderly subjects and those with preexisting renal impairment, hypovolemia, or dehydration. There is general consensus that hydration protocols implemented before and after imaging with contrast medium may be effective in preventing contrast medium–induced nephropathy. However, definitive and convincing data related to amounts to be infused, infusion timing, and type of solutions (half-isotonic, isotonic saline solution, or bicarbonate) are lacking. Forced diuresis with furosemide or mannitol and use of dopamine, together with concomitant hydration, have been proved to be ineffective or even more risky in the event of inadequate maintenance of euvolemia. Various direct or indirect vasodilators have been investigated (atrial natriuretic peptide, calcium channel blockers, angiotensin-converting enzyme inhibitors, and endothelin receptor antagonists), yet results have been inconsistent and inconclusive. Recent large meta-analyses concerning the protective role of antioxidant action of *N*-acetylcysteine have led to the conclusion that the statistical significance of the results is borderline. Preventive hemodialysis has not proved to be useful; on the contrary, it might worsen the clinical conditions by inducing hypotension. Hemofiltration, despite some positive studies, is too complex and cannot be used extensively.**

Conclusions: **It is believed that prevention is actually achieved by correcting hypovolemia, dehydration, or both. Normalization of body fluids is probably the true objective to be achieved by preventive measures in all patients, not only in those at risk. Because limited data have been collected in intensive care units, at present, no firm or specific recommendations can yet be provided for the critically ill. (Crit Care Med 2006; 34:2060–2068)**

KEY WORDS: contrast nephropathy; osmolality; hydration; acetylcysteine; fenoldopam; dialysis

Contrast medium–induced nephropathy (CMIN) is the third leading cause of hospital-acquired acute renal failure and is generally described as an acute decrease in renal function after intravascular administration of contrast media (CM) in the absence of any other cause. It is specifically defined as an absolute increase in serum creatinine values of $\geq$0.5 mg/dL (or 44 μmol/L) or a $\geq$25% relative increase from baseline within 48–72 hrs after a diagnostic or interventional procedure (1). Clinical experience has led to the understanding that certain patients have a higher predisposition to develop CMIN due to the presence of nonmodifiable risk factors arising from their pathophysiologic conditions and the presence of modifiable risk factors such as the selection and use of CM for enhancement.

Preexisting renal impairment is associated with the highest risk for developing CMIN (2). The risk seems to increase

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even further when creatinine clearance values are <60 mL/min. There is a significant relationship between an increasing baseline level of serum creatinine and the frequency of CMIN, varying from 2% in patients with baseline creatinine of <1.5 mg/dL to 20% in those with levels of >2.5 mg/dL, other risk factors being equal (3). Permanent impairment of renal function requiring dialysis can occur in up to 10% of patients with preexisting renal failure who develop a further reduction in renal function after coronary angiography (4) or in <1% of all patients who undergo percutaneous coronary intervention with CM (5). It is necessary to make a distinction between CMIN and the atheroembolic syndrome that may occur after angiographic procedures, the latter caused by cholesterol microemboli precipitation after a trauma on atherosclerotic vessels. This syndrome is characterized by acute renal failure, distal digital ischemia, livedo reticularis, and abdominal pain due to intestinal ischemia. The presence of cholesterol microvascular emboli is necessary for a histologic diagnosis (6). Acute or subacute decrease in renal function is a frequent complication of critical illness, and its prevalence among intensive care units (ICUs) reaches up to 15% (7).

There is no consensus regarding the role of advancing age as a risk factor (8): the high prevalence of CMIN in elderly patients is most likely multifactorial in origin and may be attributable to senile nephroangiosclerosis, panvasculopathy, and the difficulty in gaining vascular access through winding and calcified vessels during angiographic procedures, a condition typically seen in the elderly. Elderly patients with reduced muscular mass typical of advanced age have a decreased creatinine clearance, even when serum creatinine values are normal (9). For example, creatinine clearance measured using the Cockcroft and Gault method (9), which predicts the daily urine creatinine excretion given the age, weight, and sex of the patient, assumes that an 80-yr-old patient who weighs 60 kg and has a serum creatinine value of 0.9 mg/dL should have a creatinine clearance of almost 55 mL/min if the patient is a man and 50 mL/min if the patient is a woman, and not 120 mL/min as one could believe.

Contrary to the evidence that links advanced age to CMIN, the sex of the patient does not seem to be an important predisposing factor for CMIN. The greater prevalence of renal impairment after percutaneous coronary intervention observed in women seems due to their baseline lower glomerular filtration rate (GFR) rather than to their sex (10).

The medical community has known since the 1970s that patients with impaired renal function and diabetes are at a greater risk for developing CMIN than kidney-impaired patients without diabetes. It should be emphasized that the risk of developing CMIN in diabetic patients with normal renal function and without concomitant predisposing factors is similar to that of healthy subjects (11). In addition, when values of proteinuria are in the normal range, diabetes mellitus does not seem to be a decisive risk factor. Although there is no definitive evidence that relates the increased rate of CMIN to the duration of preexisting diabetes or to suboptimal glycemic control, adequate glycemic control should be achieved with dietary and pharmacologic therapy before administration of a CM to diabetic patients, as acute hyperglycemia can lead to direct renal damage (12).

In the past, multiple myeloma has been considered a risk factor for the development of CMIN, but this seems doubtful because the administration of CM rarely induces an increase in serum creatinine in nondehydrated patients with plasmacytoma, as dehydration is the main risk factor for CMIN (13).

Another clinical condition frequently seen in the elderly is heart failure associated with a low ejection fraction, which reduces renal perfusion and may worsen CM-induced ischemia. ICU patients with volume depletion caused by any condition, including reduced cardiac output, septic or hypovolemic shock, hypoperfusion, hypotension, or liver disease associated with significant dysproteinemia and hypoalbuminemia, would be more at risk for CMIN (8).

The same is true in cases of proteinuria, although the role of this factor in the predisposition to CMIN is still doubtful, especially as an isolated risk factor. When proteinuria exceeds 300 mg/24 hrs, there is frequently a concomitant disease, such as primary or secondary nephropathy, nephrotic syndrome, or sustained arterial hypertension (14). The statement that isolated proteinuria is a risk factor *per se* should be accepted with caution, better still with skepticism, as it is highly probable that it is due to the failure to diagnose a concomitant condition and is an index of high risk in any case.

Similarly, no definitive evidence has been provided showing that severe hypertension (≥180/100 mm Hg) is an independent risk factor for developing CMIN (15), despite a recent article (16). Hypertensive patients frequently have preexisting morphofunctional alterations of renal vessels that promote CM-induced vasospasm. Also, frequently they have diabetes, nephropathy, or both, which renders it difficult to isolate the role of elevated blood pressure *per se* in the pathogenesis of CMIN. There are no definitive results confirming that hyperuricemia, hypercholesterolemia, and low hematocrit (17) induce a predisposition to CMIN. The same is true for peripheral arterial disease and renal transplantation.

Recently, some recapitulatory tables of these risk factors have been developed to compute predictive scores and evaluate global individual probability of CMIN in patients who undergo percutaneous coronary interventions (18, 19).

Overlap of risk factors for development of CMIN is very common, even in ICU patients, frequently affected by hypovolemia, heart failure, and preexisting or acute renal failure. Concomitant therapy with potentially nephrotoxic drugs, such as aminoglycosides, vancomycin, and amphotericin B, can further increase the risk of CMIN. Nonsteroidal anti-inflammatory drugs reduce GFR in some individuals, especially in the elderly, because of the antiprostaglandin effect that may impair the normal physiologic intrarenal prostaglandin vasodilatation (20).

Type and Dose of CM

The most important modifiable risk factors to prevent CMIN are the type and dose of the CM. Actually, the so-called nonionic low-osmolal CMs still have an increased osmolality compared with plasma (600–850 mOsm/kg), whereas the newest nonionic radiocontrast agents have a lower osmolality, approximately 290 mOsm/kg, isoosmolal to plasma.

There are conflicting results regarding the administered volume of CM vs. nephrotoxicity, and definitive cut-off doses have not been established. For patients with impaired renal function, the maximum dose of CM that can be safely administered has traditionally been calculated according to the following formula: 5 mL × kg of body weight (maximum, 300 mL)/serum creatinine (in milligrams per deciliter) (21). This formula was historically validated for calculating doses of

diatrizoate, an old ionic, high-osmolal CM. Subsequently, a correction multiplying factor of 1.5 was established for nonionic, low-osmolal monomeric CMs (21), which seem to be less nephrotoxic than the old ionic, high-osmolal agents, at least in patients with preexisting renal impairment (22).

At present, there is not definitive evidence of the presumed advantage derived from the use of iso-osmolal dimers in comparison with all of the nonionic low-osmolal monomers (23), inasmuch as at present major comparative studies have been performed only vs. the monomer iohexol, which seems to be more nephrotoxic than iso-osmolal dimer iodixanol (24, 25), at least in diabetic patients with serum creatinine concentrations of 1.5–3.5 mg/dL who had undergone angiography (24). In the absence of additional large-scale, multiple-center, randomized trials, CMIN rates with most of the nonionic low-osmolal agents in high-risk patients could be comparable with rates with iso-osmolal dimer iodixanol (13, 20, 23, 26, 27).

Concerning the route of administration, a much lower prevalence of CMIN has been recorded after intravenous administration of CM in comparison with the intraarterial route (28). Injection into the renal arteries or the abdominal aorta near the origin of the renal vessels results in a higher concentration of CM in this area and therefore in higher toxicity in comparison with intravenous administration (1).

Repeated CM administration in a short period of time may increase the risk of CMIN (29). Two hours after administration, CM internalization induces cytoplasmic vacuolization and lysosomal alterations in the proximal tubule and in the internal cortex, with concomitant enzymuria. The time for the morphofunctional reconstruction of renal tubular cell integrity ranges from hours to days, depending on the extent of the toxic insult and on the condition of the renal parenchyma before the contrast procedure (30, 31). Therefore, although there is no evidence in the literature based on data from controlled trials, it is probably prudent to allow from 72 hrs to a few days between CM administrations (32, 33). It is, in any case, important to wait until renal function is completely restored before giving a second dose of CM if the first CM administration caused an increase in serum creatinine, even if no direct correlation exists between the degree of vacuolization in the tubular cells and the reduction in renal function (34, 35).

Possible Mechanisms of CMIN

The most recent scientific research, derived from preclinical studies on animals and some studies on humans, has not yet increased the knowledge of the pathogenic mechanisms underlying CMIN. Some authors maintain that the administration of CM would be followed by a phase of prolonged vasoconstriction that would lead to an increase in intrarenal vascular resistances, a reduction of the total renal plasma flow, and a decrease in the GFR (20).

The increase of diuresis and natriuresis, after the injection of compounds with elevated osmolality or tonicity, would determine the activation of so-called tubuloglomerular feedback, directly responsible for the vasoconstrictive response and sustained by the endothelin system (36).

The action of synthesis and release of nitric oxide and prostaglandins in the regulation of renal perfusion is also known. Conditions in which the reduced availability of these mediators may exist, such as during the course of CM administration, could predispose to nephropathy. Endothelial dysfunction observed in experimental models of CMIN could in part be due to the generation of oxygen free radicals during postischemic reperfusion (20, 36).

Finally, direct cytotoxicity of CM to the tubular cells seems to be confirmed by reduction of transepithelial resistances, increased membrane permeability, cytoplasmic vacuolization, and apoptotic processes detectable after administration of these compounds (20, 36).

The principal pathophysiologic mechanisms that are believed to lead to CMIN are summarized in Figure 1.

Facts and Fallacies Concerning the Prevention of CMIN

Correction of Hypovolemia or Dehydration. It is recommended to plan procedures in advance to allow time to activate prevention in high-risk patients for whom it may not be possible to avoid CM administration. Attempts to reduce the prevalence of CMIN are centered on an accurate evaluation of modifiable risk factors, an adequate patient hydration, the elimination of CM as soon as possible from the body, and the opportunity for

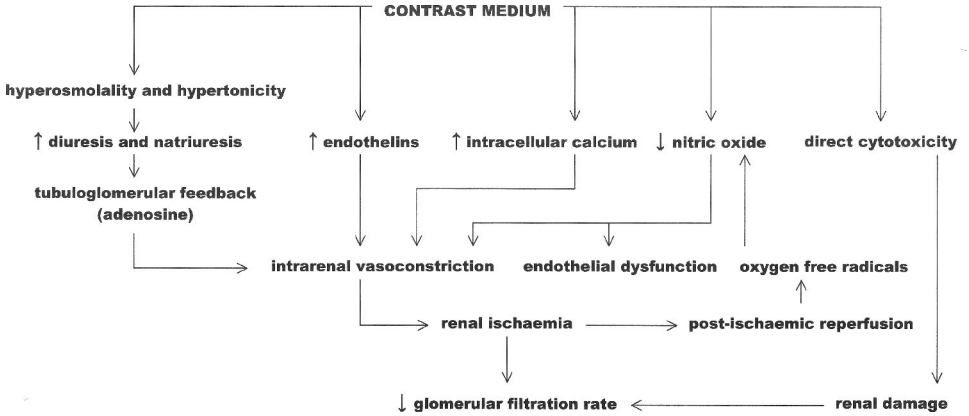

Figure 1. Possible mechanisms of contrast media–induced nephropathy. The tubuloglomerular feedback, activated by the increase in diuresis and natriuresis secondary to the injection of high osmolality, tonicity compounds, or both, determines an increase in renal resistance with subsequent renal ischemia and reduction in glomerular filtration rate. The endothelin receptors seem to be involved in the increase in vascular resistance. The endothelial dysfunction that promotes contrast media–induced nephropathy is partially due to oxygen free radical generation during postischemic reperfusion. Direct cytotoxicity of contrast media on tubular cells seems to be supported by the reduction in transepithelial resistance, membrane permeabilization, increased cytoplasmic vacuolization, and increased apoptotic processes observed after contrast media administration.

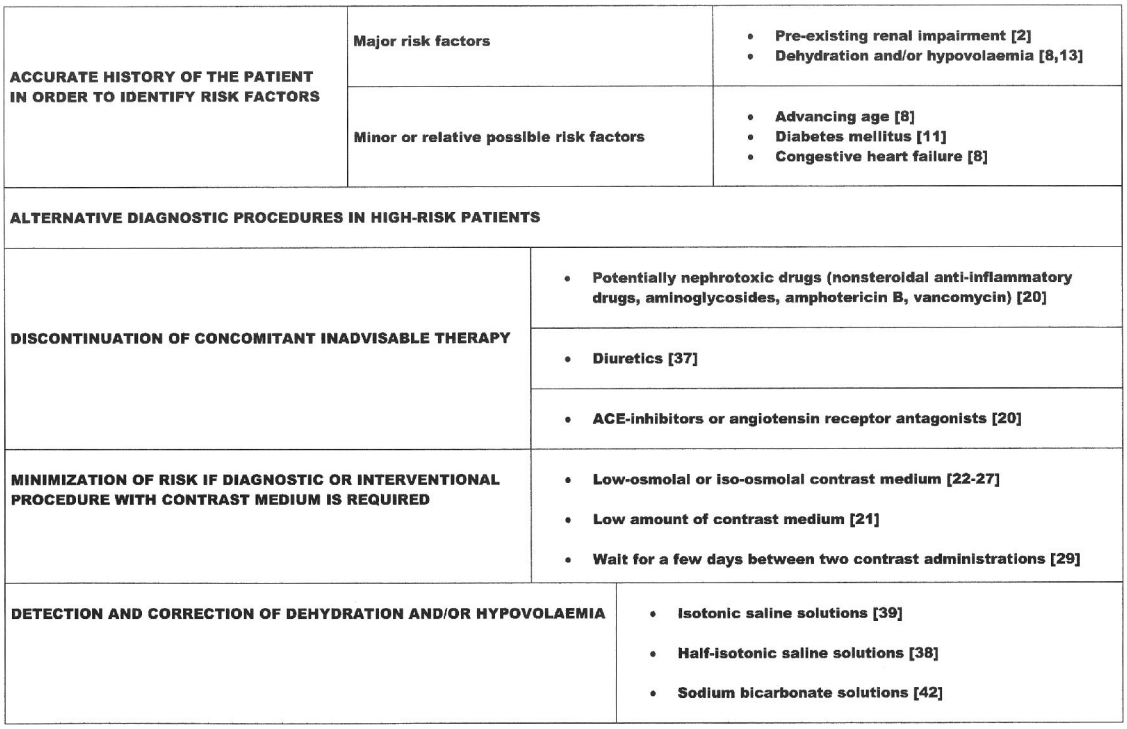

Figure 2. Proposed recommendations for prophylaxis of contrast media-induced nephropathy. Volemic expansion stimulates diuresis, dilutes contrast media and vasoconstriction mediators, and prevents tubuloglomerular and renin–angiotensin feedback activation, factors that contribute to the increase of intrarenal vascular resistances. Forced diuresis with volemic expansion by administering mannitol and furosemide intravenously seems to be less effective in comparison with simple hydration. Controversial results or no univocal consensus for the prevention of contrast medium–induced nephropathy have been attributed to low doses of dopamine and to fenoldopam, calcium-antagonists, adenosine receptor antagonists, and *N*-acetylcysteine. Citations are in brackets. *ACE,* angiotensin-converting enzyme.

pharmacologic prevention of nephrotoxic effects.

Possible prophylactic options are summarized in Figure 2, which results from a critical synthesis of all of the most recent and relevant clinical trials (1985 to January 2006), selected review articles, short communications, and letters to editors in the medical literature.

Blood volume expansion is a simple technique that reduces the prevalence of acute renal damage in patients who must undergo coronary angiography. Blood volume expansion stimulates diuresis, dilutes circulating CM and vasoconstriction mediator concentrations, and thus prevents activation of the tubuloglomerular feedback and of the renin-angiotensin system. Otherwise, both systems would contribute to an increase in intrarenal vascular resistances.

Volume expansion can be obtained with an intravenous infusion of a half-isotonic solution (1 mL/kg body weight/hr 0.45% saline), started 12 hrs before the diagnostic or interventional procedure and continued until 12 hrs postprocedure (37), or with an 0.9% saline solution (38), which could be more efficacious ($p = .04$) (39). This simple prevention technique has limitations in older patients at risk for congestive heart failure, whose hemodynamic conditions should be monitored through the evaluation of diuresis, heart rate, arterial pulse, and arterial and central venous pressure.

Hydration protocols are recommended for planned cardiac procedures for which patients should be hospitalized $\geq$12 hrs before the intervention, but a home oral hydration protocol has been proposed for selected patients (with serum creatinine between 1.4 and 3.0 mg/mL or an estimated creatinine clearance between 25 and 60 mL/min, with good hemodynamic conditions). It consists of drinking $\geq$1000 mL of H_2O in a 10-hr period before the scheduled cardiac catheterization, followed by intravenous volume expansion in hospital, for a total of 6 hrs, starting 30–60 mins before administration of the contrast agent (40).

Recently, low prevalence of CMIN after coronary intervention has been confirmed applying a combination of intravenous and oral volume supplementation (41).

Hydration has been achieved also with the administration of sodium bicarbonate. In a comparison between intravenous saline solution and sodium bicarbonate in 118 patients with serum creatinine of $>$1.1 mg/dL, sodium bicarbonate (154 mEq/L) was administered as a bolus of 3 mL/kg/hr for 1 hr before the procedure. This was followed by an infusion of 1 mL/kg/hr for 6 hrs after the procedure (42). In this study, administration of sodium bicarbonate seems to provide greater nephroprotective benefits ($p = .02$), probably due to increased flow and local tubular alkalinization and to partial correction of ischemic acidosis induced at this level.

Even in the lack of randomized controlled studies of comparisons between different types of fluids, it seems to be crucial to choose those that are able to distribute themselves in the intravascular compartment, which is the main condition for adequate renal perfusion.

Forced Diuresis. The idea that effective prevention of CMIN can be achieved through adequate hydration and forced diuresis is derived by analogy from treatments for other toxic nephropathies, in which increased rates of diuresis with maintained volume expansion result in preservation of renal function by reducing the duration of nephron exposure to the toxic agent. This could result in acceleration of tubular flow, shortened intratubular residence of the CM, reduced

CM-induced hypoxic damage, and less endothelin-mediated vasoconstriction.

The induction of forced diuresis through volume expansion and intravenous administration of mannitol and furosemide was proposed as a possible method for the prevention of CMIN in patients with chronic renal failure until the mid-1990s. However, the approach seems less effective than simple hydration ($p = .01$–$.05$) (37). In a prospective randomized study of approximately 100 patients with serum creatinine levels of about 2.5 mg/dL (221 μmol/L) who were undergoing coronary angiography, the prevalence of CMIN in the control group, which received only intravenous hydration, was similar to that in the study group, which received low doses of furosemide and dopamine, with or without mannitol, in addition to hydration. Despite the failure to detect any demonstrable effect of furosemide, dopamine, and mannitol in preventing the occurrence of CM-induced creatinine increase, the study revealed a correlation between a urinary flow of >150 mL/hr in the first 24 hrs after CM injection and a modest reduction in renal damage (43). Once again, it was impossible to establish with any certainty whether the drugs employed concomitantly with volume expansion had any truly protective role. It is possible that the absence of any benefits in the prevention of CMIN with diuretics is due to secondary effects of these agents. Mannitol, for example, may increase the intrarenal secretion of adenosine, which may then act as a potent vasoconstrictor, reducing renal plasma flow. In view of these inconclusive data, it is worthwhile to bear in mind the theory that the hypovolemia caused by diuretics, especially by furosemide, may induce or aggravate nephropathy due to CM, particularly when prompt rehydration is not ensured. Therefore, it is of basic importance to pay attention to the occurrence of orthostatic arterial hypotension, pulsus parvus, tachycardia, central venous pressure reduction, and oligoanuria as hypovolemic variables, particularly in critically ill patients.

Pharmacologically Induced Renal Vasodilatation. The administration of low doses of dopamine (2.5 μg/kg/min), starting 2 hrs before interventional coronary angioplasty and continuing for the following 12 hrs, did not significantly reduce the prevalence of CMIN after the procedure (44). One of the most probable explanations for the failure of this prophylactic strategy is the preferential vasodilatation that the drug induces in cortical arterioles, which can accentuate the CM-induced medullar hypoxia and ischemia.

A selective agonist of D_1 dopamine receptors, fenoldopam, is able to increase renal blood flow both in the cortex and in the medulla: its vasodilatory effect is six times greater than that of dopamine due to the lack of interactions with D_2 and α- and β-adrenergic receptors, responsible for vasoconstriction. Moreover, this drug could be responsible for the increase in GFR and diuresis. The protective effect of fenoldopam has been examined in diabetic patients with impaired renal function undergoing coronary angiography, and it seemed to be effective in the prevention of CMIN (45); however, there is no general consensus that fenoldopam is effective in the prevention of CMIN (46) because in other studies it was not more effective in preventing CMIN than simple hydration (47). For this reason, fenoldopam is thus no longer recommended for prophylaxis of CMIN.

Natriuretic atrial peptide has been proposed as a prophylactic agent in view of its ability to increase renal blood flow. In a multiple-center, double-blind, randomized, placebo-controlled study, intravenous administration of anaritide, a synthetic analog of human natriuretic atrial peptide, before, during, and after the diagnostic procedure did not reduce the prevalence of CMIN in patients with chronic renal failure, independently of the presence or absence of diabetes (48).

Calcium channel blockers produce vasodilatation, blocking calcium entrance into the smooth-muscle cell, also in renal arterioles, where these drugs seem to offer cytoprotection from hypoxic or toxic damage. Experimental studies conducted with verapamil and diltiazem in rats with acute renal ischemia suggest that these drugs might reduce the risk of CMIN via the attenuation of adenosine-mediated vasoconstriction; moreover, it seems that these drugs may prevent the reduction of nitric oxide synthesis that occurs in humans after CM administration. In clinical practice, the protective effect should be dose dependent. However, the studies on the efficacy of diltiazem, nitrendipine, nifedipine, amlodipine, and felodipine in humans did not provide any convincing or definitive data regarding the prevention of CMIN, and large-scale investigations are necessary before they can be routinely recommended (49–51).

Adenosine is involved in the pathogenesis of CMIN because it is able to produce vasoconstriction of the afferent arterioles, vasodilatation of the efferent arterioles, and contraction of mesangial cells. Experiments have shown that this mediator produces vasoconstriction in the renal cortex and vasodilatation in the medulla (52); moreover, adenosine seems to be involved in the production of free radicals by tubular cells and in the tubuloglomerular feedback mechanism. It has been hypothesized that nonselective receptor antagonists of adenosine, such as theophylline and aminophylline, could play a role in the prevention of CMIN also by acting as scavengers of hydroxyl radicals and inhibitors of superoxide release. Even if recent meta-analyses seem to attribute a positive effect to prophylactic administration of these agents (53, 54), other studies conducted on this topic have not provided consistent or definitive results (55–57), nor did they yield precise information on the optimal dosage and administration route in clinical practice.

Studies conducted on *in vivo* and *in vitro* models of renal ischemia have indicated the role of prostaglandin E_1 in the protection of tubular epithelial renal cells from hypoxia, independently of hemodynamic and inflammatory mechanisms. Possible cytoprotective effects in CM-induced nephropathy have been evaluated, and the vasodilatory effects may also be beneficial in preventing renal damage. The parenteral administration of different doses of prostaglandin E_1 seemed to reduce the further increase in serum creatinine after the CM infusion in patients with preexisting chronic renal failure (58, 59), but further studies are needed.

It has been observed that CMs induce an increase in endothelin (ET) production in endothelial cell cultures and that they increase its plasma concentration in humans, dogs, and mice. A nephroprotective capacity seems to be attributable to opposition to ET-mediated renal vasoconstriction: experimental studies conducted on isolated rat kidneys have shown that ET receptor antagonists could play a role in the prevention of CMIN (20, 36). However, in a study conducted in patients with chronic renal failure undergoing cardiac angiography, the administration of a nonselective ET antagonist proved to be associated with an increase in CMIN (60): the choice of a nonselective receptor antagonist, in fact, could result in predominant vasoconstriction. Whereas ET_A receptors produce vasoconstriction, ET_B

receptors produce vasodilatation and catalyze the clearance of ET itself. Moreover, to evaluate the real preventive effect of this drug, it is necessary to verify whether its plasma concentration is really significant when the risk of CMIN is at its maximum (i.e., at the time of contrast exposure).

Because angiotensin II activation could be partially involved in the intrarenal vasoconstriction mechanisms, the pharmacologic inhibition of this mediator produced by angiotensin-converting enzyme inhibitors or the more recent angiotensin receptor antagonists could be effective in the prophylaxis of CMIN. This hypothesis is supported by some experimental studies, but clinical trials are needed. In fact, in clinical practice, the administration of these drugs in patients with preexisting renal failure (clearance creatinine of ≤35 mL/min) may produce considerable reductions in GFR, especially in the elderly, in conflict with experimental findings (61).

In summary, given the lack of homogeneous and incontrovertible results in human trials, at present, vasodilators have failed to gain wide use as a preventive measure of CMIN in clinical practice.

Antioxidant Agents and Other Recent Findings. *N*-acetylcysteine is a mucolytic agent used in chronic bronchitis and as an antidote to the hepatotoxic damage caused by acetaminophen. Its role in the synthesis of intracellular and extracellular glutathione could make it a significant factor in the protection against CMIN via the prevention of oxidative stress and renal hemodynamic regulation, producing an increase in renal medullary blood flow. Its antioxidant properties depend on the reduction in the generation of free radicals by damaged cells achieved through its scavenging activity. As a reactive sulfhydryl compound, it combines with nitric oxide to produce *S*-nitrosothiol, which is more stable than its precursor and is probably a more potent vasodilator. Lastly, it may increase the expression of nitric oxide synthetase (62). In view of the competition between *N*-acetylcysteine and the superoxide radical, the production of peroxynitrite—a reactive species with oxidative and nitrosative effects on sulfhydryl groups and on the aromatic rings of proteins, on the lipids of cellular membranes, and on nucleic acids—could be limited (62). *N*-acetylcysteine could oppose cell death induced by the reperfusion and ischemia in the kidney, liver, and lungs. Similar evidence also seems to have been produced after angioplasty. This could occur via interference with signal transduction mechanisms leading to cellular apoptosis, probably triggered by oxidant agents.

It is controversial whether *N*-acetylcysteine administration could reduce the risk of CMIN significantly (63). In a study on >80 patients with renal function impairment (mean serum creatinine of about 2.4 mg/dL or 216 μmol/L) and undergoing computer tomography with CM, the addition of *N*-acetylcysteine (600 mg by mouth, twice daily, the day before and the day of the radiologic investigation, for a total of 2 days of treatment) to intravenous volemic expansion was more effective than hydration alone ($p < .001$) (64). Similar significant results were obtained from a double-blind, randomized, placebo-controlled study carried out on 54 patients with cardiac catheterizations ($p < .0001$) (65). *N*-acetylcysteine seemed to exert a protective effect also in a more recent study in 200 patients undergoing coronary angiography and with preexisting renal function impairment (creatinine clearance of <60 mL/min) ($p = .001$) (66). Finally, the intravenous administration of the antioxidant agent (*N*-acetylcysteine 150 mg/kg in 500 mL of isotonic saline solution 30 mins before the investigation, followed by 50 mg/kg in 500 mL of isotonic saline solution in the subsequent 4 hrs) could also offer some advantages in patients at risk of CMIN, provided that they are able to tolerate the required volume load ($p = .02$) (67).

On the contrary, in an investigation on 183 subjects who underwent coronary or peripheral angiography or angioplasty, and in whom a similar prophylactic approach was adopted, 6.5% of the patients premedicated with *N*-acetylcysteine had an increment in serum creatinine by ≥25% vs. baseline values, compared with 11% of the patients in the control group. The analysis of the results, obtained by stratifying for the administered CM dose, did not show significant differences between patients who received a dose of CM of >140 mL, independently of the adoption of the prophylactic protocol with the antioxidant agent (68). In comparison with simple hydration, the inefficacy of prevention with *N*-acetylcysteine, administered by mouth (1200 mg 1 hr before the procedure and 1200 mg 3 hrs after it), together with intravenous hydration, also seems to have been demonstrated in a study on 79 patients with chronic renal impairment who underwent cardiac angiography (69).

Recently, a higher prophylactic effect of a double dose of *N*-acetylcysteine (1200 mg orally, twice daily, before and after coronary or peripheral procedures) than a standard dose (600 mg orally, twice daily, before and after coronary or peripheral procedures) along with half-isotonic saline hydration has been reported (70).

In summary, the usefulness of *N*-acetylcysteine employment in various regimens and doses has not been uniformly demonstrated by more recent trials (71), and the best route of its administration is uncertain (72). The numerous meta-analyses carried out on the large number of studies on this topic show that *N*-acetylcysteine might really reduce the prevalence of CMIN (73–76), but the results are barely significant and have been extrapolated from trials that are very heterogeneous in terms of methods.

Moreover, it is very important to exclude any direct effect of *N*-acetylcysteine on the laboratory determinations of the principal renal function indices because significant decreases in mean values of serum creatinine and increases in GFR 4 hrs after the administration of the last dose of *N*-acetylcysteine (after 600 mg every 12 hrs, for a total of four doses) have been recorded in patients who had not received any CM. At elevated concentrations of *N*-acetylcysteine (50 g/L), it is possible to find a 50% reduction in serum creatinine that is simply dependent on analytical interactions in the determination of serum levels of creatinine (77–79).

A recent article shows the use of ascorbic acid as antioxidant agent with a reduction of CMIN prevalence in subjects with renal failure undergoing coronary procedures, but large-scale trials are needed to confirm these preliminary data (80).

Finally, a report seems to confirm that statins might provide clinically positive effects in the renal vasculature through antioxidant, anti-inflammatory, and antithrombotic properties: preprocedure statin use is associated with reduction in CMIN after percutaneous coronary intervention (81).

Hemodialysis and Hemofiltration. Although iodinated CMs are effectively eliminated from the body by hemodialysis, the use of this technique after the CM administration in patients with preexisting renal impairment has been shown to have no significant effect on CMIN (82). Also, the preventive employment of hemodialysis is not useful in the approach

to CMIN due to the rapid onset of this disorder, even if dialysis is applied very early (83). On the contrary, the procedure worsens renal function, probably on account of the hypotensive episodes that it may produce, which are triggered by the activation of inflammatory reactions associated with release of vasoactive substances. This is particularly true in critically ill patients, who are often in unstable hemodynamic conditions. Moreover, the nonionic osmolality of CMs is higher than plasma osmolality, and their presence in the vascular compartment produces an increase in plasma volume by osmosis. The removal of CM by dialysis can produce a shift of free H_2O in the opposite direction (i.e., from the vascular compartment to the interstitium and intracellular space), with plasma volume depletion, possibly followed by a reduction in renal blood flow caused by activation of vasoconstrictor mechanisms. It should be borne in mind that many factors can contribute to the higher or lower clearance of the CM by hemodialysis, such as flow rate, type of membrane, and also in relation to the kind of CM used.

Continuous venovenous hemofiltration (CVVH), started 4–8 hrs before and continued for 18–24 hrs after CM administration, seemed to reduce the prevalence of CMIN in a study conducted on 114 patients with chronic renal impairment (mean creatinine clearance of about 26 mL/min) undergoing diagnostic and therapeutic coronary interventions (84). A decrease in renal function was found to occur, with lower prevalence in the continuous venovenous hemofiltration group in comparison with the control group, in which isotonic saline hydration alone had been performed. Indeed, the study in itself is not exempt from criticisms, owing to the presence of possible confounding factors (for example, the relative alkalinization consequent to procedure being *per se* theoretically beneficial in the prophylaxis of CMIN and the higher intensity of care received by continuous venovenous hemofiltration patients in the ICU setting). Even if the maintenance of a regular renal perfusion deriving from the relative hemodynamic stability during this replacement treatment could be consistent with continuous venovenous hemofiltration employment to prevent CMIN, the complexity of the technique, which must be performed at specialized centers (i.e., renal ICU), and its costs must be taken into consideration in general clinical practice. Thus, this procedure is not highly recommended in the approach to CMIN.

Prevention of CMIN in Critically Ill Patients: Conclusion and Recommendations

Observation and clinical practice have established a few undeniable points for the prevention of CMIN: a) the fact that not all CMs are equally nephrotoxic; b) the necessity of an accurate history of individual patients to identify the subjects at high risk because of concomitant conditions or diseases; c) the importance of administering CM doses tailored to the individual patient (i.e., to the minimum useful amount to reduce renal toxicity); and finally, d) wait between two CM administrations for a long enough period to ensure the resolution of vacuolar degeneration of the tubular cells and restoration of enzyme activity—that is to say, cellular function.

These general medical recommendations should be extended to ICU clinical practice, even if at present it is impossible to quantify the entity of CMIN in ICUs because no data are available on the exact prevalence of CM renal damage in critically ill patients (85).

When a patient is at risk of CMIN, it is important to institute preventive measures and use the least toxic compounds, as the risk is always difficult to quantify. Unfortunately, the pharmacologic agents used to prevent CMIN have yielded discouraging and unconvincing results or, at most, partial results that require further supporting evidence.

At the moment, the most convincing procedure is hydration of the patient at risk. This procedure at least prevents dehydration, the tendency toward hypovolemia, and the activation of the mechanisms responsible for vasoconstriction. It is still not clear which solutions should be given priority (i.e., isotonic saline, half-isotonic saline, or sodium bicarbonate solutions). The most effective prophylactic system is probably volume correction independently of the quality of the infused fluid, the importance of which may be marginal.

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