Contrast Media Induced Nephropathy in Patients Undergoing Cardiac Catheterisation

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Cardiovascular diseases constitute the first cause of death in patients with chronic renal failure (CRF)[1]. The main condition responsible for the high cardiac mortality in the above patients is ischaemic heart disease[2], which is attributed to the markedly elevated prevalence of systemic hypertension (96%), diabetes mellitus (DM-54%), low plasma HDL concentration (33%), elevated plasma concentrations of oxidized LDL, fibrinogen and homocysteine and finally, to the advanced age of the CRF patients[3,4]. Indeed, patients with end-stage renal failure (ESRF) have a 5-20-fold greater prevalence of coronary artery disease (CAD) as compared to the general population. The prevalence of CAD is lower in patients with mild impairment of renal function (38%), and markedly higher in those with end-stage renal disease undergoing chronic haemodialysis or peritoneal dialysis (67%), especially when comorbidities (such as DM) are present[2,5,6].

Definition of chronic renal failure

In most studies including patients with CRF, the variable selected for their classification into subgroups according to the degree of renal function impairment is the serum creatinine (Cr). However, at present, an absolute consensus for the definition of CRF according to a single cut-off point for Cr serum concentration has not been established. It seems that a Cr serum concentration above 1.5 mg/dL, with a Cr clearance below 60 mL/min/1.73 m^2, distinguishes patients with impaired and normal renal function[7,8]. According to the report of the National Health and Nutrition Examination Survey (where the serum Cr levels in 18,723 healthy individuals aged 12 years and older were examined between 1988 and 1994), the mean serum Cr value was 0.96 mg/dL for women and 1.16 mg/dL for men[7]. Cr levels of 1.5 mg/dL or greater were seen in 9.74% of men and 1.78% of women[7]. Mean serum creatinine values were higher in older persons and depended on the sex, body weight (variables used for the estimation of the Cr clearance), and on the ethnicity[7]. As a result, according to this report, it is concluded that the use of a single cut-off point to define elevated serum creatinine values may be misleading.[7]

Diagnostic evaluation of coronary artery disease in patients with chronic renal failure

Regarding the diagnostic evaluation of coronary artery disease in patients with CRF, neither the clinical presentation nor the commonly used diagnostic methods (such as electrocardiography and thallium scintigraphy) have a satisfactory sensitivity and specificity, with a possible exception being dobutamine echocardiography[4]. As a result, when coronary artery disease is strongly suspected on clinical grounds, coronary arteriography is often strongly recommended. However, in patients with CRF, the intravascular administration of contrast agents in the

setting of cardiac catheterisation, especially when coronary angioplasty is performed (which implies higher total volumes of contrast medium), causes further impairment of renal function in a percentage of 10-20% of patients (range 5-50% in the various studies)[9-12]. The above condition is described as Contrast Induced Nephropathy (CIN), or Radiocontrast Nephropathy (RCN)[9-12]. In the general population, the incidence of CIN has been calculated to be less than 2%[13].

Definition of contrast induced nephropathy and predisposing factors for its development

CIN is defined as an increase in the base-line serum Cr concentration of at least 0.5 mg/dL (or ≥25%) within 48 hours after the injection of radiocontrast agents (with slight variations concerning Cr rise being reported in older studies)[10,14-16]. In fewer than 1% of patients who develop CIN chronic dialysis is required[9]. In any case, CIN constitutes an unfavourable event which is associated with prolonged hospitalisation and with increased short and long term morbidity and mortality rates[17]. In a study where patients with CRF underwent percutaneous coronary interventions and developed CIN requiring dialysis, the in-hospital mortality was 22.9%[18].

Most elevations in Cr concentrations in the setting of CIN are nonoliguric[9]. Cr serum levels peak within 24-72 hours and they gradually return to the baseline levels within 2 weeks[9,16]. Conditions that predispose to CIN development, apart from preexisting CRF (with the risk of CIN being particularly high for serum Cr levels >2.0 mg/dL or Cr clearance <47 mL/min), include DM, volume depletion, heart failure (ejection fraction <35% and/or NYHA classification III or IV), chronic liver diseases, multiple myeloma, contemporaneous administration of nephrotoxic medications (particularly aminoglycosides and non steroidal anti-inflammatory medications), and the total contrast volume. With contrast volumes >3 mL/kg of body weight there is a high incidence of CIN, whereas its incidence is minimal when a total contrast less than <100 mL is administered[9,10,16,19-23]. It must be stressed that diabetic patients receiving metformin, who require intravascular administration of iodinated contrast media, must temporarily discontinue the drug, as the eventuality of contrast induced renal failure can result in lactic acidosis[24,25]. According to the current guidelines metformin must be withheld after the administration of the contrast agent for 48 hours, and can be restarted if renal function is not affected at 48 hours[25].

Concerning the contrast medium, the incidence of CIN, apart from the total contrast volume as already mentioned, is influenced by the chemical structure and particularly by the osmolarity and the ionic (or non-ionic) structure of the contrast agent used[16,26,27]. Initially, it seemed that non-ionic contrast agents (containing 6 iodine anions in their molecule) were less nephrotoxic than ionic contrast agents (containing 3 iodine anions in their molecule). However, in a recent study where 443 patients were randomly assigned to a non-ionic (iopamidol) and an ionic (diatrizoate) contrast agent, the incidence of CIN was not statistically different (8.2 and 10.2% respectively)[26]. With regard to the osmolarity of the contrast medium 3 generations of agents are currently available. The first generation agents are extremely osmolar ionic monomers, the second generation ones are non-ionic monomers with substantially lower osmolarity (but still hyperosmolar relative to plasma) and, finally, the third generation agents are non-ionic dimers and are isoosmolar relative to plasma[27]. The impact of the contrast agent osmolarity on CIN development has been investigated in a multicentre study that enrolled 123 patients undergoing coronary arteriography or aortofemoral angiography. The contrast media administered were the third generation (isoosmolar) agent iodixanol and the second generation agent iohexol[16]. The mean increase in Cr was 0.13 mg/dL in the iodixanol (third generation agent) group and 0.55 mg/dL in the iohexol group ($p=0.001$). This study showed that CIN is less likely to develop in high risk patients when iodixanol, a third generation isoosmolar non-ionic dimer, is used. However, the Editorial that comments on the aforementioned study emphasises the need for additional clinical studies to further elucidate this important problem[27].

Pathogenetic mechanisms

The precise mechanism by which CIN occurs is unclear, since there is no satisfactory animal model of contrast agent induced nephropathy[25]. Among the various mechanisms proposed, the most probable include a rapid and sustained reduction in renal plasma flow preferentially to the outer medulla, direct toxic damage to renal tubular epithelial cells caused by generation of oxygen free radicals, and the

caspase-dependent apoptotic renal cell damage[9,10,27-29]. Concerning the first mechanism, experimental data suggest that arteriolar vasoconstriction (which causes plasma flow reduction) is mediated by a local delivery of endothelin-1 and, in part, by activation of the renin-angiotensin-aldosterone system[27,30-33].

Prevention

A) Non-pharmaceutical strategies

For the prevention of CIN several strategies have been proposed and applied, with the results often being conflicting. This is probably due to methodological differences between the various studies[27]. At present, among the preventive measures, intravenous prehydration remains the most safe, the most widely applied and probably the most effective[34]. A large number of studies, with several being prospective and randomised, have shown the clinical benefit of hydration, whose effectiveness is actually considered to have been definitely proved[32]. For CIN prevention normal saline is administered at a rate of 1ml/kg of body weight/hour for 12 hours before the radiocontrast procedure and for 6-12 hours after the last dose of radiocontrast (dosage titration is required in cases of congestive heart failure)[35,36]. Apart from normal saline, other intravenous solutions have been used to test their effectiveness regarding CIN prevention. In one study, 1,620 patients scheduled for percutaneous coronary angioplasty were randomly assigned to receive isotonic (0.9% saline) or half-isotonic (0.45% sodium chloride plus 5% glucose) hydration[37]. The results of this investigation showed that isotonic hydration is superior to half-isotonic hydration in the prevention of CIN (incidence 0.7% vs. 2% respectively, p=0.04). In another study, in 36 patients with mild to moderate CRF undergoing elective cardiac catheterisation, an inpatient versus outpatient hydration protocol was assessed[36]. The patients enrolled were randomised to receive either intravenous hydration (0.45 normal saline solution at 75 mL/h for both 12 h precatheterisation and post-catheterisation) or an outpatient hydration protocol including precatheterisation oral hydration (1,000 mL clear liquid over 10 h) followed by 6 h of intravenous hydration (0.45 normal saline solution at a rate of 300 mL/h) beginning just before contrast administration. The maximal changes in serum Cr in the inpatient and outpatient groups were comparable, which means that hospital admission for intravenous hydration is unnecessary before elective cardiac catheterisation in the setting of mild-to-moderate renal dysfunction. However, the above study included a small number of patients and further studies are required to confirm the effectiveness of the outpatient hydration protocol. Furthermore, in a similar study, the benefit of oral hydration was not confirmed[35]. As a result, the current practice consists of hospitalisation of the patients with CRF undergoing elective cardiac catheterisation with administration of normal saline at a rate of 1ml/kg of body weight/hour for 12 hours before the procedure and for 12 hours after the last dose of contrast agent.

In an effort to prevent CIN in patients with impaired renal function at high risk, alternative angiographic contrast agents have been used. In a relevant study gadopentetate dimeglumine, a gadolinium-based contrast medium used in magnetic resonance, was administered to 29 high-risk patients undergoing diagnostic or interventional angiographic procedures[38]. Gadopentetate dimeglumine had sufficient radiographic density to allow adequate diagnostic visualisation. Only one of the patients had evidence of post-procedure CIN (incidence of approximately 3%). The results of this study are certainly encouraging but the small number of patients enrolled must be taken into account for the final conclusions. Moreover, no data concerning the visualisation of the coronary arteries are available, given that the study dealt with peripheral vessels.

Although the ability of extracorporeal treatments after administration of contrast media to prevent radiocontrast-induced nephropathy is controversial, haemodialysis is performed in many institutions after radiographic procedures. There are conflicting reports on the efficacy of different dialysers and treatment modalities in removing contrast media[39-42]. The available data indicate that haemodialysis eliminates contrast medium effectively, but it may not influence the incidence or outcome of CIN[39]. Recently, in patients with CRF undergoing coronary arteriography, the effect of a simultaneous (on line) haemodialysis during radiocontrast medium administration (Iopremol) on renal function was investigated. The patients were randomised to receive a simultaneous high-flux haemodialysis (7 patients) or to a control group (10 patients). The clinical follow-up lasted for 8 weeks after radiocontrast medium application. Cr clearance showed no difference 1 week and 8 weeks after angiography, either from baseline or between the groups. In each group,

2 patients developed end-stage renal disease and required permanent dialysis during the 8-week follow-up. Simultaneous dialysis reduced the area under the curve of iomeprol significantly: however, it does not influence its plasma peak concentration after angiography[41]. In another study, prophylactic haemodialysis after radiocontrast media administration in patients with renal insufficiency was pro-ved not to be beneficial, but potentially even harmful[42].

In a recent study, the role of haemofiltration, as compared with isotonic-saline hydration, in preventing CIN in patients with CRF failure was investigated. The study population consisted of 114 consecutive patients with CRF (serum Cr concentration >2 mg/dL) who were undergoing coronary interventions. The patients were randomly assigned to either haemofiltration in an intensive care unit (58 patients) or isotonic-saline hydration at a rate of 1 ml/kg of body weight/per hour (56 patients). Haemofiltration (fluid replacement rate, 1000 ml per hour without weight loss) and saline hydration were initiated 4-8 hours before the coronary intervention and were continued for 18-24 hours after the procedure termination. An increase in the serum Cr concentration of more than 25% from the baseline value occurred less frequently among the patients in the haemofiltration group than among the control patients (5% vs. 50%, $p<0.001$). Temporary renal-replacement therapy (haemodialysis or haemofiltration) was required in 25% of the control patients and in 3% of the patients in the haemofiltration group. The rate of in-hospital events was 9% in the haemofiltration group and 52% in the control group ($p<0.001$), whereas in-hospital mortality was 2% and 14% respectively ($p=0.02$). The cumulative one-year mortality was 10% in the haemofiltration group and 30% in the control group ($p=0.01$)[43]. The above results showed that in patients with CRF who are undergoing percutaneous coronary interventions, periprocedural haemofiltration given in an intensive care unit setting appears to be effective in preventing the deterioration of renal function due to contrast-agent-induced nephropathy, and is associated with improved in-hospital and long-term outcomes.

B) Pharmaceutical strategies

A large list of medications has been tested for the prevention of CIN, with different and often conflicting results. The medications utilized include N-acetylcysteine, fenoldopam, dopamine, prostaglandin E1, mannitol, furosemide, SB 290670 (endothelin A and B receptor antagonist), nifedipine, felodipine, captopril, theophylline, aminophylline, and atrial natriuretic peptide (anaritide). The first two drugs, where the experience is much greater, will be discussed in depth below. Concerning the rest, negative results (with a higher incidence of CIN) were observed with the use of endothelin A and B receptor antagonist SB 290670, neutral results (no effect on CIN incidence) with the use of mannitol, furosemide, nifedipine, felodipine, aminophylline and anaritide, whereas conflicting results were observed with theophylline and dopamine[14,44-52]. In contrast, favourable results were recorded with prostaglandin E1 (infusion of 20 ng/kg/min, 60±30 min before the contrast agent administration with an overall infusion time of 6 hours) and captopril (at a dosage of 25 mg 3 times daily, for 3 days, beginning 1 hour before the procedure)[32,53]. However, the positive results of prostaglandin E1 and captopril come from small studies and require confirmation from large, adequately powered multicentre trials.

As already mentioned, sufficient data regarding CIN prevention are currently available only for N-acetylcysteine and fenoldopam. N-acetylcysteine is an antioxidant that might prevent, at least in theory, acute contrast nephrotoxicity caused by the generation of oxygen free radicals, which are involved in CIN development[30]. Acetylcysteine has been shown to attenuate ischaemic renal failure in animals[54]. It has been orally administered for CIN prevention at a dosage of 400-600 mg (usually 600 mg) twice daily on the day before and on the day of administration of the contrast agent, for a total of 2 days. Three doses are given before and one dose after cardiac catheterisation[54,55]. Clinical studies of N-acetylcysteine in the prevention of CIN in patients who are undergoing elective diagnostic and/or interventional coronary angiographic procedures, have yielded highly mixed results; five were dramatically positive, and eight others had no demonstrable efficacy at all[56]. However, in two recent meta-analyses, acetylcysteine significantly reduced the risk of CIN[57,58]. In the first acetylcysteine reduced the relative risk of contrast nephropathy by 56% ($p=0.02$) compared with periprocedural hydration alone[57], whereas in the second the overall relative risk for CIN associated with the use of acetylcysteine was 0.41 ($p=0.007$)[58]. The conflicting results of acetylcysteine, as with some

of the above mentioned medications, are probably due to methodological differences, such as different base-line values of Cr, different total contrast volumes, different prevalence of comorbid conditions in the study population (mainly DM), and finally, different additional periprocedural treatment. At present, the beneficial effect of acetylcysteine on CIN prevention has not been definitely demonstrated. Its effectiveness is probably limited to the subgroups of patients who are at low risk for CIN development[34].

The second drug that has been widely studied is fenoldopam, which is a novel parenteral vasodilator. Fenoldopam activates dopamine A1 receptors (DA 1)[10], which are particularly prominent in the renal and peripheral vasculature[10,59]. DA-1 receptor stimulation in the peripheral vessels causes a decrease in blood pressure due to the decrease of the peripheral resistances[59]. In the renal vasculature, fenoldopam induces vasodilation in a dose-dependent manner, causing an increase of blood flow to the renal cortex and the outer medulla, both in healthy individuals and those with CRF[9,59]. Fenoldopam has recently been approved by the U.S. Food and Drug Administration (FDA) for the in-hospital management of hypertensive crisis and perioperative hypertension. The drug has no rebound effect, and its use can be stopped at any time[59,60]. The prophylactic use of felondopam in patients at risk of CIN is based on its property of increasing blood flow in the outer medulla, an area where radiocontrast agents preferentially reduce blood flow[29]. Pilot trials of fenoldopam showed, with few exceptions, very promising results concerning its safety and effectiveness in CIN prevention[12,59,61,62]. As a result, a prospective randomised placebo-controlled trial was conducted to verify its prophylactic effect on renal function[10]. For that purpose 45 patients with CRF who were undergoing contrast angiography were randomly assigned to fenoldopam or placebo. The primary endpoint was a change in renal plasma flow 1 hour after contrast infusion, while the secondary endpoint was the incidence of CIN, defined as a 0.5 mg/dL or a 25% rise in serum Cr level at 48 hours. Fenoldopam was given intravenously at a rate of 0.1 μg/kg/min for 5 hours, beginning at least 1 hour before the infusion of the contrast dye. Renal plasma flow was found to be significantly higher in the fenoldopam group, whereas only a trend (without a statistically significant difference) was noticed between the two groups concerning CIN development. The above study was followed by the prospective, multicentre, randomised and placebo controlled CONTRAST trial, which included 315 patients with CRF (not in dialysis) who were undergoing cardiac catheterisation with or without angioplasty[11]. All patients were well hydrated and randomised to either intravenous fenoldopam (0.05 g/kg/min titrated up to 0.10 g/kg/min) or matching placebo starting 1 hour before angioplasty and continuing for 12 hours thereafter. The primary end point of the study was incidence of CIN, defined as an increase in serum creatinine of >25% from baseline during a 96-hour period. The results of the trial were presented at the scientific sessions of the American College of Cardiology in 2003, held in Chicago. The number of patients who reached the primary end point of the study did not differ between the felondopam- and placebo-treated patients (36.6% vs. 30.1% respectively, p =0.54). Nor was any difference in Cr elevation detected in the various subgroups of the study population. The drug was discontinued, due to side effects, in 13.4% of fenoldopam-treated patients compared with 7% of placebo-treated patients. From this study, which is the largest to date, it was concluded that fenoldopam is ineffective in preventing further renal function deterioration in patients with CRF who receive contrast agents intravascularly, and should not be used for this application. The negative finding of this investigation also suggests that disturbances in intrarenal haemodynamics may not be the critical pathophysiologic insult that produces CIN.

Conclusions

CIN constitutes a common and potentially serious complication of intravascular contrast media administration in the setting of cardiac catheterisation and/or or percutaneous coronary interventions. Patients with pre-existing renal failure and DM are at particularly high risk. Nephropathy induced by exposure to radiocontrast agents is associated with significant in-hospital and long-term morbidity and mortality. At present, the mainstay against CIN development is adequate prehydration. Limitation of total contrast volume is also of critical impor-tance. Other strategies, such as use of an isoosmolar, dimeric, non-ionic contrast medium and prophylactic N-acetylcysteine administration, appear to be promising approaches, but further multicentre trials should be conducted to prove their efficacy conclusively. Concerning acetylcysteine, its low cost, ease of

administration and limited adverse effects are all reasons to consider its administration before contrast media administration and to investigate its role in CIN prevention further[63]. Finally, periprocedural haemofiltration given in an intensive care unit setting appears to be effective in preventing the deterioration of renal function due to contrast-agent-induced nephropathy and is associated with improved in-hospital and long-term outcomes[43].

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