Contrast media-induced nephropathy: case report and review of the literature focusing on pathogenesis

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Abstract

Contrast media administration during diagnostic and invasive procedures in high risk patients for nephrotoxicity is a common problem in clinical practice. The mechanisms involved in renal function impairment after contrast media administration are not precisely known but are intensively investigated, and new data have emerged in the literature lately. We present the case of a 72-year old male patient with diabetic nephropathy to whom a new generation iso-osmolar contrast medium (iodixanol) was administered during intravenous pyelography. Due to the contrast agent administration, the patient developed irreversible acute renal failure and became dialysis-dependent. This case suggests that even new generation contrast media (including iodixanol) may be severely nephrotoxic, when administered to high risk patients. Additionally we review the complex mechanisms involved in pathogenesis of contrast media nephrotoxicity. Hippokratia 2008; 12 (2): 87-93

Key words: acute renal failure, contrast media, diabetes mellitus, nephrotoxicity

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Contrast media-induced nephropathy (CIN) is defined as the acute deterioration of renal function after parenteral administration of contrast medium in the absence of any other cause1. Renal function deterioration according to most authors is referred to an increase of serum creatinine concentration of > 0.5 mg/dL (44 μmol/L) or 25% above baseline, within 48 hours after contrast medium administration.

The incidence of CIN in the general population has been estimated to be less than 2%2. However in high-risk patients the incidence can rise to more than 50%. CIN represents the third most frequent cause of hospital acquired acute renal failure. Pre-existing renal impairment and diabetes mellitus have been identified as the main conditions predisposing to the development of CIN. Other risk factors include advanced age (> 75 years), decreased effective blood volume (heart failure, liver cirrhosis, nephrotic syndrome), use of diuretics, non-steroid anti-inflammatory drugs (NSAIDs) and other nephrotoxic medications, peripheral vasculopathy, anaemia, hypercholesterolemia, previous parenteral contrast medium administration within 72 hours and large volume of contrast medium2.

It is estimated that during 2003 approximately 80 million parenteral doses of iodinated contrast media were administered worldwide, corresponding to approximately 8 million litres of contrast medium. During the last two decades the number of computed tomographies has increased by 800% and between 1979 and 2002 the number of percutaneous cardiac interventions in the USA has risen by 390%. As the number of susceptible patients exposed to parenteral iodinated contrast media expands, contrast-induced nephropathy represents an ever-growing clinical problem. Meanwhile, the main predisposing factors for CIN, namely diabetes mellitus and previous renal impairment are currently augmented. Thus, the estimated increase in renal insufficiency incidence by 2010 in the USA is 90% and the incidence of diabetes mellitus, currently affecting 192 million people worldwide, is expected to rise 75% by 20254.

An intravenous pyelography in 1919 was the first reported parenteral application of an iodinated contrast medium5, and acute renal failure following intravenous pyelography in a patient with myelomatosis in 1954 was the first reported case of CIN6. First generation contrast agents were ionic monomers containing a benzene ring with three iodine atoms, exhibiting high osmolarity in the range of 1500 to 1800 mOsm/kg (High Osmolar Contrast Agents). Alleged nephrotoxicity related to high osmolarity led to the development of non-ionic monomers, reducing osmolarity by half (Low Osmolar Contrast Agents) but still exhibiting more than double the osmolarity of plasma. Third generation agents are dimers almost isoosmolar to plasma (Isoosmolar Contrast Agents) but with increased viscosity, which results in complicated injection through small vascular catheters. Nevertheless even third generation contrast agents have been implicated by
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He had been smoking for the last 40 years and had hypertension, treated with atorvastatin. He also had hypercholesterolemia and treated with atorvastatin. He also had type 2 diabetes mellitus, diagnosed before 15 years and treated with insulin the last 4 years.

He had been hospitalized in another facility for 3 days before admission to our department, complaining of weakness, nausea and fatigue. Laboratory investigation revealed renal insufficiency (serum creatinine Cr: 2 mg/dL). An intravenous pyelography had been performed using an inexplicably large dose (320 mg) of ioxan (Visipaque) as contrast medium. Intravenous pyelography had shown no signs of lithiasis or obstruction. The patient left the clinic two days after the pyelography. Renal function had not been reevaluated after administration of the contrast medium.

On admission the patient had signs of pulmonary edema (dyspnea, tachypnea, use of auxiliary respiratory muscles, rales in the lower fields of both lungs). Clinical examination revealed hypertension (160/70 mmHg) and tachycardia (96 beats per min). The patient had normal sinus rhythm. A loud systolic murmur was audible in the auscultatory area of the aortic valve. Loud systolic murmurs were also audible over the carotid arteries, the abdominal aorta and the femoral arteries. Pulses in the pedal areas and posterior tibial arteries were palpable.

Electrocardiogram showed left anterior hemiblock and incomplete right bundle branch block. On rectal examination mild enlargement of the prostate gland without tenderness was found. Examination of the ocular fundi showed signs of diabetic retinopathy (microaneurysms, retinal hemorrhages and exudates). Laboratory investigation showed the following: Hematocrit: 38.5%; Hemoglobin: 13.1 g/dL; White Blood Cell Count: 10200/μL (Neutrophils: 74%; Lymphocytes: 15%; Monocytes: 7%; Eosinophils: 4%); procalcitonin: 171 mg/dL; serum creatinine: 7.8 mg/dL; total protein: 5.3 g/dL; serum albumin: 2.3 g/dL; fibrinogen: 314 mg/dL; ESR: 32 mm; CRP: 11 mg/L; CPK: 154 IU/L; ALT: 22 IU/L; AST: 28 IU/L. Arterial blood gas examination was consistent with metabolic acidosis and profound hypoxia (pH=7.34; pCO₂=26 mmHg; pO₂=70 mmHg; Oxygen saturation: 91%; HCO₃⁻=14 mmol/L). Chest X-ray was diagnostic of pulmonary edema. Urine examination showed: specific gravity: 1015; pH=7; protein: > 300 mg/dL; red blood cells: 20-30 per high power field. Urine culture was negative. Kidney size was normal (11 cm) on ultrasound examination. Finally a renal scintigraphy scan revealed significant reduction of radioactivity uptake in both kidneys and oliguric acute on chronic renal failure was diagnosed.

The patient remained oliguric after the first 6 hours. Therefore, he had to be on dialysis for managing pulmonary edema, metabolic acidosis and uremia. Acute renal failure did not regress after regular dialysis sessions and the patient underwent detailed investigation of potential underlying causes. Immunologic investigation, immunoelcrophoresis, protein immunofixation of serum and urine specimens as well as bone imaging studies were normal.

Kidney biopsy, performed after the 35th day of persisting acute renal failure, demonstrated diffuse and nodular diabetic glomerulosclerosis with concomitant signs of

Figure 1. Molecular structure of contrast media: First generation high osmolar ionic monomer iothalamate, second generation low osmolar non-ionic monomer iohexol, third generation iso-osmolar non-ionic dimmer ioxanol

some authors for potential nephrotoxicity (Figure 1).

Renal failure following exposure to radiocontrast agents is usually nonoliguric. Creatinine rises within 48 hours, peaks 4 to 5 days after exposure and returns to baseline in 7 to 10 days. Complete recovery is expected in more than 75% of patients, who develop this complication, but approximately 10% become dialysis dependent. Contrast-induced nephropathy leads to increased mortality, with an odds ratio of 5.5. Clinical experience over the last two decades has noted that the introduction of low- and iso-osmolar contrast media has resulted in decreased frequency of contrast-induced nephropathy. Especially ioxanol, a new generation iso-osmolar contrast medium, has proved to be adequately safe, even when administered to high-risk patients.

We herein present the case of an elderly patient with diabetes mellitus and slight impairment of renal function who, after intravenous pyelography with ioxanol, developed acute renal failure becoming permanently dialysis dependent. The aim of this study is to emphasize that even the last generation contrast media when administered in high risk patients could be detrimental. On the other hand we review the currently available experimental and clinical data on the mechanisms involved in pathogenesis of CIN, because we consider that these mechanisms deserve significant interest for the development of new perspectives for the prevention of CIN in the near future.

Case presentation

Our patient, 72 years old, complained of malaise, nausea, vomiting, weakness, fatigue, urine volume reduction (about 600 mL/24 h) and deteriorating dyspnea. He had been smoking for the last 40 years and had hypercholesterolemia treated with atorvastatin. He also had type 2 diabetes mellitus, diagnosed before 15 years and treated with insulin the last 4 years.

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Kidney biopsy, performed after the 35th day of persisting acute renal failure, demonstrated diffuse and nodular diabetic glomerulosclerosis with concomitant signs of
acute tubular necrosis (Figures 2,3). Acute renal failure finally progressed to end-stage chronic renal failure and the patient maintained on chronic hemodialysis.

Discussion

First generation, high-osmolar contrast media are more nephrotoxic than new generation, low- and iso-osmolar ones. Consequently, it is currently believed that these new generation contrast agents should be preferred for high risk. Two of the most widely used new contrast media, iohexol (a non-ionic, iso-osmolar dimer) and iohexol (a non-ionic low-osmolar monomer) have consistently been found adequately safe, both in intra-arterial and in intravenous administration to high-risk patients. Chalmers and Jackson found that ioxaglate was less nephrotoxic than iohexol, when administered intra-arterially to patients with renal impairment. Similarly, in the NEPHRIC study only one diabetic patient developed persistent renal failure owing to intra-arterial iohexol administration, while no case of irreversible renal failure occurred among patients who received intra-arterial iohexol. To our knowledge, irreversible renal failure that could be ascribed to ioxaglate has not been reported in the literature.

Acute renal failure was irreversible and so the patient had to start hemodialysis. This is not in accordance with the prevailing notion that permanent renal failure is associated with first-generation contrast agents rather than second-generation contrast agents. Indeed, in the Iohexol Cooperative Study acute dialysis was warranted in 5 patients with intra-arterial iohexol administration, most of whom suffered from diabetes mellitus. Similarly, in the NEPHRIC study only one diabetic patient developed persistent renal failure owing to intra-arterial iohexol administration, while no case of irreversible renal failure occurred among patients who received intra-arterial ioxaglate. To our knowledge, irreversible renal failure that could be ascribed to ioxaglate has not been reported in the literature.

Pathogenesis of CIN

Many different pathogenetic mechanisms of nephrotoxicity have been proposed, still none fully explaining the pathogenesis of CIN, which is likely to involve the interplay of several factors including alterations in renal microcirculation and medullary oxygenation, as well as direct cytotoxicity related to physicochemical and immunological properties of contrast media. Research is hampered by the fact that experimental models do not develop CIN unless renal circulation or function are already compromised, and by the unavailability of simple techniques, which would allow evaluation of renal parenchymal hypoxia and tubular damage detection.

It seems that the kidney area mainly affected by the administration of contrast media is the already hypoxic renal medulla and especially the deeper portion of the outer medulla, corresponding to the thick ascending limbs of the loop of Henle. This area is highly susceptible to hypoxic injuries e.g. when the kidney is perfused with erythrocyte-free medium. It is the area where the countercurrent mechanism of urine excretion control is maintained at the expense of hypoxia, with pO$_2$ levels falling as low as 20 mmHg. This is the result of a distinct parallel disposition of tubules and vasa recta, which maximizes urine concentration by countercurrent exchange but also allows for oxygen diffusion from arterial to venous vasa recta. Impaired oxygen supply in combination with in-
increased oxygen requirements by the active reabsorption of sodium, render this area extremely vulnerable to hypoxic injuries. The main proposed pathogenetic mechanisms of CIN involve a) the exacerbation of medullary hypoxia due to altered haemodynamics, which in the presence of impaired adaptive responses leads to tubular damage and b) a direct cytotoxic effect of the radiocontrast agents on tubular cells.

Microcirculation / Oxygenation

Experimental models of animals predisposed to ischemic injury have demonstrated that after parenteral administration of contrast media they exhibit short-term renal vasodilatation, which is followed by prolonged vasoconstriction, resulting in a decrease in total renal blood flow (RBF) and a reduction of glomerular filtration rate (GFR).

There are regional differences in blood flow alterations between renal cortex and medulla, which are further affected by the availability of vasodilators such as nitric oxide (NO) and prostaglandins. In their presence the infusion of contrast media leads to an increased blood flow in the outer medulla. Pharmacologic inhibition of prostaglandin and NO synthesis by indomethacin (cyclooxygenase inhibitor) and L-NAME (N-nitro-L-arginine methyl ester, NO synthase inhibitor) decreases blood flow in the aforementioned area. The blood flow reduction results in increased hypoxia, which is further exacerbated by the increased energy requirements in the ascending loop, induced by an osmotic diuresis effect of contrast media.

Among many other agents, endothelin-1 (ET-1) and adenosine seem to play an important role in the alteration of blood flow in the renal microcirculation after contrast media administration.

Endothelin-1 and contrast media

Gurbanov et al. have demonstrated that ET-1 decreases cortex renal blood flow in normal rats while increasing the blood flow into the medulla. Unselective inhibition of ET_{A} and ET_{B} receptors by bosentan blocked the medullary vasodilatation caused by ET-1, which was in turn induced by a specific ET_{B} receptor agonist (IRL-1620), indicating that medullary vasodilatation by ET-1 may be mediated by activation of ET_{B} receptors. In the same experiment medullary vasodilatation by ET-1 was completely or partially inhibited by NO synthase or cyclooxygenase inhibition respectively, pointing out the dependence of ET-1 vasodilatatory effect on the availability of NO and to a lesser extent of prostaglandins.

Administration of radiocontrast agents in normal rats induces endothelin release, as has been indicated by the experiments of Heyman et al., both in vivo (rats) and in vitro (bovine endothelial cells). Infusion of hypertonic solutions of mannitol, NaCl or glucose did not have that effect. Renal medullary hypoxia seems to be ameliorated by ET_{A}-receptor inhibition, even though the effect may involve tubular transport mechanisms rather than haemodynamic alterations.

In a radiocontrast nephropathy model induced in rats by the injection of indomethacin, L-NAME and iothalamate, Bird et al. demonstrated that unselective ET_{A}/ET_{B}-receptor inhibition and selective ET_{A}-receptor inhibition attenuated the fall in RPF and GFR as well as tubular cell necrosis, caused by the contrast agent.

However in humans with chronic renal insufficiency exposed to radiocontrast agents for coronary angiography, unselective endothelin receptor antagonism actually exacerbated radiocontrast nephrotoxicity, irrespective of systemic blood pressure drop, probably because of altered intrarenal haemodynamic responses caused by renal failure, or due to loss of the potential renoprotective effect of medullar vasodilatation, induced by ET_{B} receptor activation. To our knowledge there are no data evaluating potential nephroprotection offered by selective ET_{A}-receptor inhibition in patients predisposed to develop contrast-induced nephropathy.

In conclusion, parenteral administration of contrast media induces endothelin release, which in the presence of already compromised renal haemodynamics (e.g. lack of NO or prostaglandins) leads to tubular necrosis, probably by exacerbating hypoxia in the outer medulla (Figure 4).

Adenosine effect on renal haemodynamics is complex and still not fully understood. Adenosine is formed mainly by dephosphorylation of 5’-adenosine monophosphate (5’-AMP) by 5’-nucleotidase, which is activated...
by intracellular energy depletion, caused by conditions such as hypoxia and ischemia. Through activation of the high affinity A<sub>1</sub> adenosine receptors (A<sub>1</sub>AR) in the afferent glomerular arteriole, adenosine induces vasoconstriction and reduction in GFR, thus being considered as the mediator of the tubuloglomerular feedback mechanisms (TGF). Supranormal levels of adenosine also activate the widely distributed low affinity A<sub>2c</sub> adenosine receptors (A<sub>2c</sub>AR), causing renal vasodilatation. Increased adenosine-induced renal vasoconstriction in combination with attenuated renal NO-dependent vasodilatation, may account for the predisposition of diabetic patients to CIN.

In an experimental model Arakawa et al. examined the effects of radiocontrast media on dog renal function with and without renal insufficiency. They found that the administration of the non-ionic contrast medium iohexol increased effective renal plasma flow (ERPF) and GFR in dogs with intact renal function, mainly through A<sub>1</sub>AR stimulation, while in subtotally nephrectomized animals it induced a marked decrease in ERPF and GFR, mainly through A<sub>1</sub>AR activation. In a more recent study Lee et al. report that A<sub>1</sub>AR knock out mice as well as mice pre-treated with a selective A<sub>1</sub>AR antagonist were protected against radiocontrast nephropathy.

Studies involving unselective adenosine receptor antagonism with theophylline for the prevention of nephropathy in susceptible patients receiving contrast agents have yielded conflicting results, failing to provide evidence of superiority over the use of low osmolar contrast agents and hydration. Lack of conclusive evidence supporting the nephroprotective properties of theophylline, combined with its potential side effects (arrhythmias, convulsions) and its narrow therapeutic range, still prohibit its use for routine prophylaxis against CIN.

**ROS**

Reactive oxygen species (ROS) and endothelial dysfunction due to oxygen free-radical generation during post-ischemic reperfusion, leading to medullary vasoconstriction, have also been implicated in the pathogenesis of CIN. Free radicals react with NO to produce peroxynitrite, and are responsible for the deactivation of NO, which results in haemodynamic alterations in the outer medulla and exacerbates ischemic cellular damage after contrast media administration. Increased production of 3-nitrotyrosine, a marker for peroxynitrite generation, has been documented following the infusion of radiocontrast agents in humans. N-acetylcysteine, a free radical scavenger with negligible side effects, is under investigation as a promising agent for the prevention of CIN, even though the results of many currently available trials are not totally conclusive.

**Cytotoxicity**

Apart from haemodynamic alterations, the direct toxicity of contrast media on proximal tubular cell is still under investigation as a major contributor to the development of CIN. Studies are mainly in vitro and involve cell cultures and isolated tubular segments. Cell vacuolization is the most commonly encountered finding, suggesting cytoplasmic injury, although is seems to be reversible and a correlation between the extent of tubular vacuolisation and the reduction of renal function has not been proven yet.

Rapid loss of cellular proteins, such as sodium-potassium ATPase pump, and mitochondrial proteins, such as cytochrome C, as well as increased susceptibility of the cell membrane to phospholipase A2, has been documented as a result of direct contact of tubular cells with contrast media. Direct cytotoxicity is also suggested by the reduction in transepithelial resistance, permeability to insulin and displacement of membrane proteins after the administration of radiocontrast agents.

Enzymuria involving N-acetyl-beta-D-glucosaminidase (NAG), alanine aminopeptidase (AAP), and microproteinuria involving alpha1- and beta2- microglobulin, both reflecting tubular damage, has been documented after contrast media administration in humans.

Activation of the complement system though the alternative pathway by direct stimulation of endothelial cells after contrast media administration has been observed in vitro. Mesangial infiltration of neutrophils and macrophages leading to mesangial contraction and reduction in GFR, may suggest another pathogenetic mechanism leading to CIN.

The association between contrast media hyperosmolality and toxicity has not been fully established yet, but is suggested by the ability of other hyperosmolar substances, such as mannitol and hypertonic saline, to induce similar morphological, structural and enzymatic alterations. There are several studies supporting the superi-
Conclusions

Contrast-induced nephropathy is an ever growing clinical problem, the pathogenesis of which still remains to be fully elucidated. Haemodynamic alterations exacerbating renal medullary hypoxia, as well as direct cellular toxicity, seem to account for the main pathogenetic mechanisms leading to acute renal failure in predisposed patients (Figure 6).

Figure 6. Summary of proposed mechanisms of contrast media-induced nephropathy. RBF: renal blood flow, NO: nitric oxide, PG: prostaglandins

Even new generation contrast media are dangerous when administered to patients at high risk for nephrotoxicity. This holds true for ioxilan, which is generally regarded as the safest contrast medium. Therefore, standard precautions to reduce frequency and severity of acute renal failure should not be neglected.

As long the interplaying pathways orchestrating the development of CIN are not precisely elucidated, and etiologic preventive measures could not be applied, the current recommendations for avoiding CIN should only include patients selection, hydration and administration of the lowest possible quantity of a low- or iso-osmolar radiocontrast agent.

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