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Review article

Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) Guidelines

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Abstract. The Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR) has looked at the effects of contrast media on the kidney including prevention of contrast medium induced nephropathy. This has resulted in four reports dealing with 1) contrast medium induced nephrotoxicity, 2) haemodialysis and contrast media, 3) use of gadolinium contrast media instead of iodinated contrast media and 4) contrast media injection in diabetic patients receiving metformin. The review presents an overview of these four reports and offers the current understanding of the interaction between contrast agents and the kidney.

In 1994 the Board of the European Society of Urogenital Radiology (ESUR) established a Contrast Media Safety Committee (CMSC) consisting of members of the Society with a major interest in contrast media research and representatives from companies, which manufacture contrast agents (during these 9 years Amersham Health, Bracco, Guerbet and Schering have been represented in the committee). Among the areas that the CMSC has looked at are the effects of contrast media on the kidney including prevention of contrast medium induced nephrotoxicity. The present review gives an overview on the various guidelines produced by ESUR on the kidney and contrast media.

Nephrotoxicity

The term contrast media nephrotoxicity is widely used to refer to the reduction in renal function induced by contrast media. It implies impairment in renal function (an increase in serum creatinine by more than 25% or 44 μmol l^{-1}) occurring within 3 days following the intravascular administration of contrast media and the absence of alternative aetiology [1].

Contrast medium induced nephrotoxicity is considered an important cause of hospital acquired renal failure. This is not surprising, since diagnostic and interventional procedures requiring the use of contrast media are performed with increasing frequency. In addition, the patient population subjected to these procedures is progressively older with more co-morbid conditions [2]. Even a small decrease in renal function due to contrast medium nephrotoxicity may greatly exacerbate morbidity caused by co-existing conditions. Sepsis, bleeding, coma and respiratory failure are frequently observed in patients with acute renal failure.

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Renal handling of contrast media

Contrast media particles after intravascular administration move across capillary membranes (except an intact blood–brain barrier) into the interstitial extracellular space. Reverse movement from the extracllular space into the intravascular compartment also occurs and a state equilibrium is generally reached within 2 h. Continuous elimination through the glomeruli also occurs. Less than 1% is excreted through extrarenal routes in patients with normal renal function [3]. The elimination half-life following intravascular administration in patients with normal renal function is about 2 h and 75% of the administered dose is excreted in urine within 4 h [4]. After 24 h 98% of the injected contrast media are out of the body. After approximately 150 min the concentration of contrast medium decreases in a monoexponential way in patients with normal renal function, but in patients with severely reduced renal function this phase is delayed [5].

Particles of contrast material are not reabsorbed by the renal tubular cells, hence they exert an osmotic force causing marked reduction of reabsorption of water and sodium from the tubules. Within minutes of an intravascular osmotic diuretic being injected, the water and sodium excretion from the kidney increases markedly. Contrast medium induced natriuresis will lead to stimulation of tubuloglomerular feedback (TGF) mechanism. Diuresis will cause an increase in intratubular pressure, which will cause reduction in the glomerular filtration rate (GFR).

Pathophysiology of contrast medium nephrotoxicity

A reduction in renal perfusion caused by a direct effect of contrast media on the kidney and toxic effects on the tubular cells are generally accepted as the main factors in the pathophysiology of contrast medium induced nephropathy. However, the importance of direct effects of contrast media on tubular cells is contentious. The mechanisms responsible for reduction in renal perfusion involve

tubular and vascular events. High osmolality contrast media (HOCM) produce marked natriuresis and diuresis that can activate the TGF response. This leads to vasoconstriction of the glomerular afferent arterioles causing a decrease in GFR and an increase in renal vascular resistance (RVR). The TGF may be responsible for almost 50% of the increase in RVR induced by high-osmolar ionic contrast media. In contrast, iso-osmolar dimers, which induce only a mild diuresis and natriuresis, do not activate this mechanism. The activation of the TGF is osmolality dependent and low osmolar contrast media, which are still hypertonic solutions compared with blood, may also stimulate this mechanism. Other possible tubular events in the pathogenesis of contrast medium induced nephropathy include an increase in the intratubular pressure and tubular obstruction by Tamm-Horsfall protein and abnormal proteins. However, there is no strong evidence to support the importance of these tubular effects in the pathophysiology of contrast medium induced nephropathy.

The structural effects of contrast media on the renal tubules include vacuolization of the epithelial cells of the proximal tubules, DNA fragmentation (abnormal activation of apoptosis or "programmed" cell death) and necrosis of the cells of the thick ascending limbs of loops of Henle in the renal medulla. Active engulfing of contrast media in tubular cells causes the vacuolar responses in the tubular cells, which cause lysosomal changes. The vacuolization is reversible and resolves within a few days of contrast medium administration. There is no correlation between the degree of vacuolization in the tubular cells and the reduction in renal function. The structural effect of contrast medium in the renal medulla is due to ischaemia and is less with low osmolar contrast media. Activation of apoptosis may play an important role in the nephron injury and renal failure induced by contrast media.

The vascular events following contrast media administration are mainly secondary to the direct renal effects of contrast media, which modulate the synthesis and release of vasoactive mediators within the kidney. The endogenous vasodilators prostaglandins and nitric oxide are not directly involved in the renal haemodynamic effects of contrast media. Nevertheless, the intrarenal production of these vasodilators is important in maintaining the perfusion and oxygen supply of the medulla, a tissue that is poorly perfused and inadequately supplied with oxygen. In situations where the synthesis of these mediators is hampered, the renal insult produced by contrast media is enhanced.

The vasoactive substances endothelin (ET) and adenosine are important in the mediation of the renal haemodynamic effects of contrast media. Contrast agents stimulate the release of ET by endothelial cells in culture and increase both the plasma ET concentration and the urinary ET excretion following intravascular administration. ET receptor antagonists may prevent the fall in GFR and the reduction in renal perfusion induced by contrast media. In addition, following contrast media administration, the increase in plasma ET is greater in patients whose renal function declines when compared with those whose renal function remains unchanged.

Adenosine is an important mediator of the reduction in GFR and renal blood flow induced by contrast media. The biological interaction between adenosine and ET is unknown [1, 6].

Clinical features of contrast medium induced nephropathy

An increase in serum creatinine and a decrease in creatinine clearance reflecting a decrease in the GFR characterize the clinical features of contrast medium induced nephropathy. The increase in serum creatinine often peaks within 3 to 4 days after the administration of contrast media [7]. Mild proteinuria and oliguria may also be observed. The majority of patients with contrast medium nephrotoxicity tend to be non-oliguric except those with pre-existing advanced chronic renal failure. Heavy proteinuria is an unusual feature of contrast medium nephrotoxicity. Fortunately, most episodes of contrast medium nephrotoxicity are self-limited and resolve within 1 to 2 weeks. Permanent renal damage is rare and occurs only in a very few instances. However, contrast medium nephrotoxicity can increase the risk of developing severe non-renal complications and prolong hospital stay [2].

Contrast media induced nephrotoxicity can be confused with the syndrome of atheroembolism that may develop after catheter angiography. This condition is not caused by contrast media, but results from trauma to the atherosclerotic blood vessels precipitating cholesterol microemboli. The clinical picture is characterized by acute renal failure associated with distal digital infarction and skin mottling. Renal histology demonstrates microvascular cholesterol emboli, which is pathognomonic of this condition.

Biochemical evaluation of contrast medium induced nephropathy

Measurement of serum creatinine can be used to monitor renal function in patients with pre-existing renal impairment before the administration of contrast media [6]. Determination of the GFR is the best sensitive test to assess renal function, but is not easy to obtain. Creatinine clearance is often used as a measurement of the GFR. However, creatinine is not a perfect marker for measuring GFR as it is both filtered by the glomeruli and secreted by the tubules.

Enzymuria from various parts of the nephron and its cells can be seen following the administration of contrast media. However, no relationship has been established between a reduction in GFR and the presence of enzymuria following the administration of contrast media [6]. Therefore, the detection of urinary enzymes is thought to be of little importance to the clinical assessment and management of contrast medium nephrotoxicity. Transient proteinuria has been observed after contrast media injection [7]. This is most likely secondary to increased leakage through the glomeruli although reduced re-absorption by the renal tubules has also been suggested. Contrast media in urine may interfere with some of the protein assay techniques leading to false positive results. This is probably a pH effect and care must be exercised in interpreting tests for proteinuria in the presence of any contrast agent in the urine.

Radiographic features of contrast medium induced nephropathy

Persistent nephrogram on plain radiography or CT of the abdomen for 24–48 h post contrast media injection has

been described as a feature of contrast medium induced nephropathy [6–8]. However, this sign is now considered non-specific and can be observed in a number of cases without nephrotoxicity [6]. However, the presence of this sign may discourage the administration of further doses of contrast media [1].

Incidence of contrast medium induced nephropathy

The development of contrast medium induced nephropathy is low in people with normal renal function varying from 0% to 5% [1, 6]. Pre-existing renal impairment increases the frequency of this complication. An incidence of contrast medium induced nephropathy ranging from 12% to 27% was reported in several prospective controlled studies [1, 2, 9]. In one study, an incidence as high as 50% was reported in patients with diabetic nephropathy undergoing coronary angiography in spite of the use of low osmolar contrast media and adequate hydration. Dialysis was necessary in 15% of these patients [10].

Long-term renal effects of contrast media

High osmolar contrast media can enhance the progression of glomerulosclerosis and renal failure in old spontaneously hypertensive male rats [11]. However, the long-term effects of contrast media on renal function in man are not known.

Predisposing factors to contrast medium induced nephropathy

The patients at highest risk for developing contrast induced acute renal failure are those with pre-existing renal impairment particularly when the reduction in renal function is secondary to diabetic nephropathy [1, 9]. Diabetes mellitus *per se* without renal impairment is not a risk factor. The degree of renal insufficiency present before the administration of contrast media determines to a great extent the severity of contrast media nephrotoxicity. Large doses of contrast media and multiple injections within 72 h increase the risk of developing contrast medium induced nephropathy. The route of administration is also important and contrast media are less nephrotoxic when administered intravenously than when given intra-arterially in the renal arteries or in the aorta proximal to the origin of the renal blood vessels. The acute intrarenal concentration of contrast media is much higher after intra-arterial injection than after an intravenous administration. Dehydration and congestive cardiac failure are risk factors as they are associated with a reduction in renal perfusion, which enhances the ischaemic insult of contrast media. Multiple myeloma has been considered in the past as a risk factor for contrast medium induced nephropathy. However, if dehydration is avoided contrast media administration rarely leads to acute renal failure in patients with myeloma.

Old age (over 60 years) is a risk factor because of the reduction in renal mass, function and perfusion, which occurs with age, predisposes the elderly patients to contrast medium induced nephropathy. The concurrent use of nephrotoxic drugs such as non-steriodal anti-inflammatory drugs (NSAID) and aminoglycosides potentiate the nephrotoxic effects of contrast media. The importance of hypertension, hyperuricaemia or proteinuria *per se* as risk factors for contrast medium induced nephropathy is not clear.

The type of contrast media is also an important predisposing factor. HOCM are more nephrotoxic in comparison with low osmolar contrast media particularly in patients with pre-existing renal impairment [6, 7, 9]. A multicentre trial of high risk patients indicate that the non-ionic dimers, which are iso-osmolar and highly hydrophilic, may be less nephrotoxic than the non-ionic low osmolar monomers [12].

Prevention of contrast medium induced nephropathy

Several measures have been recommended to prevent contrast medium induced nephropathy [12], which include:

- volume expansion
- hydration with intravenous administration of normal saline (NaCl 0.9%) or half strength saline (NaCl 0.45%)
- infusion of mannitol
- administration atrial natriuretic peptide
- loop diuretics
- calcium antagonists
- theophylline
- dopamine
- acetylcysteine
- dopamine-1 receptor antagonist fenoldopam
- use of low-osmolar non-ionic contrast media instead of high-osmolar ionic contrast media
- use of iso-osmolar non-ionic contrast media instead of low-osmolar non-ionic or high-osmolar ionic contrast media
- haemodialysis rapidly after contrast administration
- injection of small volume of contrast medium
- gadolinium based contrast media instead of iodine based contrast media for radiography
- avoiding short intervals (less than 48 h) between procedures require intravascular administration of contrast media.

Of all these measures, extracellular volume expansion and use of low osmolar contrast media were found to be most effective [1, 9, 13, 14]. An advantageous effect of the use of iso-osmolar non-ionic contrast media in patients with diabetic nephropathy has recently been shown in one study [12], however, more studies are required to validate this observation. Patients with pre-existing renal impairment or multiple myeloma should be adequately hydrated prior to contrast medium administration.

Volume expansion can be achieved with the intravenous injection of 100 ml h^{-1} of 0.9% saline starting 4 h prior to contrast medium administration and continued for 24 h [9, 13]. This regimen is suitable for patients who are not in congestive heart failure and are not allowed to drink or eat prior to undergoing an interventional or surgical procedure. If there is no contraindication to oral administration, free fluid intake should be encouraged. At least 500 ml of water or soft drinks before and 2400 ml during the following 24 h should be offered orally; in hot climates higher fluid intake should be offered. This fluid intake should secure a diuresis of at least 1 ml min^{-1}.

Table 1. European Society of Urogenital Radiology simple guidelines to avoid contrast medium nephrotoxicity [1]

Definition		Contrast medium nephrotoxicity is a condition in which an impairment in renal function (an increase in serum creatinine by more than 25% or 44 μmol l^{-1}) occurs within 3 days following the intravascular administration of a contrast medium (CM) in the absence of an alternative aetiology.
Risk factors	Look for	•Raised S-creatinine levels, particularly secondary to diabetic nephropathy •Dehydration •Congestive heart failure •Age over 70 years old •Concurrent administration of nephrotoxic drugs, *e.g.* non steroidal anti-inflammatory drugs
In patients with risk factor(s)	Do	•Make sure that the patients is well hydrated [give at least 100 ml (oral, *e.g.* soft drinks, or intravenous (normal saline) depending on the clinical situation) per hour starting 4 h before to 24 h after contrast administration – in hot climates increase the fluid volume] •Use low- or iso-osmolar contrast media •Stop administration of nephrotoxic drugs for at least 24 h •Consider alternative imaging techniques, which do not require the administration of iodinated contrast media
	Do not	•Give high osmolar contrast media •Administer large doses of contrast media •Administer mannitol and diuretics, particularly loop diuretics •Perform multiple studies with contrast media within a short period of time

In addition to volume expansion and the use of non-ionic low-osmolar contrast media, concurrent administration of nephrotoxic drugs such as gentamicin and NSAID should be avoided. Administration of frusemide and mannitol is no longer recommended [1, 13, 14]. A guideline on how to diminish the risk of contrast medium induced nephropathy has recently been proposed by the CMSC of the ESUR (Table 1).

The effectiveness of the prophylactic administration of renal vasodilators such as theophylline and calcium antagonists in prevention of contrast medium induced nephropathy remains contentious. However, in one recent study the administration of 200 mg theophylline was shown to offer a preventive effect [15]. The antioxidant acetylcystine was found to be very effective in preventing contrast medium induced nephropathy in two small studies [16, 17] and not effective in a third study [18]. Recently the dopamine-1 receptor agonist fenoldopam was shown to reduce the incidence of contrast medium induced nephrotoxicity in patients with renal impairment undergoing percutaneous coronary intervention [19]. Further studies are required before the protective effect of these various drugs is conclusively proven.

Dialysis has been used in the prevention of contrast medium induced nephropathy. Haemodialysis and peritoneal dialysis safely remove both iodinated and gadolinium based contrast media from the body [20]. The effectiveness of haemodialysis depends on many factors including blood and dialysate flow rate, permeability of dialysis membrane, duration of haemodialysis and molecular size, protein binding, hydrophilicity and electrical charge of the contrast medium. Generally several haemodialysis sessions are needed to remove all contrast medium, whereas it takes 3 weeks for continuous ambulatory dialysis to remove the agent almost completely. There is no need to schedule the dialysis in relation to the injection of iodinated or MR-contrast media or the injection of contrast agent in relation to the dialysis program. Haemodialysis does not protect poorly functioning kidneys against contrast medium induced nephropathy [21]. In addition, haemodialysis may cause deterioration of

Table 2. European Society of Urogenital Radiology (ESUR) simple guidelines on dialysis and contrast media administration [14]

	Recommendations
Haemodialysis [all contrast media can be removed by haemodialysis]	Avoid osmotic and fluid overload Correlation of the time of contrast media injection with the haemodialysis session is unnecessary Extra haemodialysis session for removal of contrast media is unnecessary
Continuous ambulatory peritoneal dialysis (CAPD) [all contrast media can be removed by peritoneal dialysis]	*X-ray examinations*: To protect residual renal function please refer to ESUR guidelines to avoid contrast medium induced nephrotoxicity Hydration should be considered only after careful evaluation of fluid balance state of the patient Haemodialysis is not recommended *MR-examinations:* To protect residual renal function use only doses up to 0.3 mmol kg^{-1} body weight of gadolinium based contrast agents Haemodialysis is not recommended
Patients with severely reduced renal function	Please refer to ESUR guidelines to avoid contrast medium induced nephrotoxicity (hydration, use small doses of low osmolar contrast media) Haemodialysis is unnecessary In MRI examinations avoid doses more than 0.3 mmol kg^{-1} body weight of gadolinium based contrast agents

Table 3. European Society of Urogenital Radiology (ESUR) position statement on the use of gadolinium-based contrast media for radiographic examinations [21]

Legal position	Gadolinium-based contrast media are not approved for X-ray examinations
Uses of gadolinium-based contrast media for X-ray examinations reported in the literature	•Significant renal impairment •Prior severe generalized adverse reaction to iodinated contrast media •Imminent thyroid treatment with radioactive iodine
ESUR position	1. The use of gadolinium based contrast media for radiographic examinations is not recommended to avoid nephrotoxicity in patients with renal impairment since they are more nephrotoxic than iodinated contrast media in equivalent X-ray attenuating doses 2. The use of gadolinium based contrast medium in approved intravenous doses up to 0.3 mmol kg^{-1} body weight will not give diagnostic radiographic information in most cases

renal function through activation of inflammatory reactions with the release of vasoactive substances that may induce acute hypotension. The CMSC of the ESUR has recently released its simple guidelines on the use of dialysis after administration of contrast media (Table 2).

It has been suggested that gadolinium-based contrast media could replace iodinated contrast media for radiological examinations in patients with significant renal impairment to reduce the risk of contrast medium nephropathy [22]. According to experimental data gadolinium-based contrast media have more nephrotoxic potential than iodinated contrast media in equivalent X-ray attenuating doses. Therefore gadolinium-based contrast media should not replace iodinated contrast media in patients with renal insufficiency for radiographic examinations. Gadolinium-based contrast media are not approved for radiographic examinations. The CMSC of the ESUR has recently released its position on the use of gadolinium based contrast media for radiographic examinations (Table 3).

Metformin-induced lactic acidosis and the intravascular administration of contrast media

The biguanide metformin (dimethylbiguanide) are used in non-insulin dependent diabetes mellitus. Approximately 90% of metformin is eliminated via the kidneys in 24 h. Renal insufficiency (GFR$<$70 ml min^{-1}, or serum creatinine $>$140 μmol l^{-1}) will lead to retention of these biguanides in the tissues and the potential for the development of fatal lactic acidosis [23].

The use of contrast media in patients receiving metformin should be carried out with care. Contrast media can induce a reduction in renal function, which occurs after the contrast medium has reached the kidney (see above), leading to retention of metformin that may induce lactic acidosis. There is no conclusive evidence indicating that the intravascular use of contrast media precipitated the development of metformin induced lactic acidosis in patients with normal S-creatinine ($<$130 μmol l^{-1}). The complication has almost always been observed in non-insulin dependent diabetic patients with abnormal renal function before injection of contrast media.

Serum creatinine should always be monitored to check that it is within the normal range before administration of metformin is resumed in order to avoid metformin being administered to a patient with abnormal renal function ($>$130 μmol l^{-1}) due to contrast medium induced nephropathy. In many countries metformin is only approved for use in patients with normal renal function. The CMSC of the ESUR (Table 4) has produced a new guideline on the use of metformin and contrast media.

Treatment of contrast medium induced nephropathy

The treatment of contrast media induced nephropathy begins with recognition of the condition. For high risk

Table 4. European Society of Urogenital Radiology (ESUR) guidelines for the administration of contrast media to diabetics taking metformin [23]

1. Serum creatinine level should be measured in every diabetic patient treated with biguanides prior to intravascular administration of contrast media. Low-osmolar contrast media should always be used in these patients.
2. Elective studies

a) If the serum creatinine is normal, the radiological examination should be performed and intake of metformin stopped from the time of the study. The use of metformin should not be resumed for 48 h and should only be restarted if renal function/serum creatinine remains within the normal range.

b) If renal function is abnormal, the metformin should be stopped and the contrast study should be delayed for 48 h. Metformin should on be restarted 48 h later, if renal function/serum creatinine is unchanged.

3. Emergency cases

a) If the serum creatinine is normal, the study may proceed as suggested for elective patients.

b) If the renal function is abnormal (or unknown), the physician should weigh the risks and benefits of contrast administration. Alternative imaging techniques should be considered. If contrast media administration is deemed necessary and the following precautions should be implemented:

•Metformin therapy should be stopped

•The patient should be hydrated, *e.g.* at least 100 ml h^{-1} of soft drinks or intravenous saline up to 24 h after contrast medium administration – In warm areas more fluid should be given

•Monitor renal function (serum creatinine), serum lactic acid and pH of blood

•Look for symptoms of lactic acidosis (vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnoea, lethargy, diarrhoea and thirst). Blood test results indicative of lactic acidosis: pH$<$7.25 and lactic acid $>$5 mmol

patients measurement of serum creatinine between the 2nd and 4th day post-procedure will identify the non-oliguric form of contrast medium induced nephropathy. In the oliguric patient, a 24-h urine volume <400 ml will trigger the diagnosis. There is no specific treatment for contrast medium induced nephropathy.

Haemodialysis should be used only if clinically indicated. The acute management of contrast medium induced nephropathy is the similar to that for patients with acute renal failure due to other causes and should include careful monitoring of serum electrolytes to detect hyperkalaemia, meticulous attention to fluid intake and output to prevent hypovolaemia or hypervolaemia, daily serum creatinine measurements, daily weights plus adequate nutritional intake. Attempts to convert oliguric renal failure to the non-oliguric form using mannitol and frusemide have been unsuccessful. The patient should not be re-exposed to contrast media before the kidney function has returned to its previous function. If contrast is to be given again, the patient must be adequately hydrated.

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