MDCT and Contrast Media: What are the Risks?

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Introduction

With the advent of multi-detector computed tomography (MDCT) technology, the number of patients undergoing contrast-enhanced CT (CECT) studies has steadily grown in the last 6 years. In 2005, approximately 22 million CECT examinations were carried out in the European Union, and 32 million in the United States (*The Imaging Market Guide 2005. Arlington Medical Resources, Inc., Philadelphia, PA*). Unfortunately, post-contrast-material-related adverse events, i.e., all those unintended and unfavorable signs, symptoms, or diseases temporally associated with the use of an iodinated contrast material (CM), are a common occurrence in radiology departments. Most adverse events occur within the first 60 min following CM administration ("immediate" or "acute" adverse events), with the greatest risk in the first 20 min. More-delayed CM adverse events also occur, with some recorded up to 7 days post-contrast administration ("delayed" or "late" events) or even later ("very late" adverse events). Adverse reactions to CM can also be classified as "renal" if the signs and symptoms are caused by CM-induced kidney damage, or they may be "non-renal". Some subjects are at higher than usual risk for the development of post-CM complications. Risk factors can be usually identified prior to the CECT exam; some are modifiable, but all require specific measures to reduce or minimize the rate and severity of adverse events. This chapter addresses and discusses the most common risk factors for adverse reactions to CM and provides practical recommendations aimed at improving the safety of CECT procedures.

Renal Adverse Reactions

Contrast-material-induced kidney damage is immediate, starting as soon as the first CM molecule reaches the kidney; however, it takes several hours or days for a deterioration of renal function to be detected.

Despite more than 30 years of research, the pathophysiology of CM-induced nephropathy (CIN) is poorly elucidated. Nonetheless, several risk factors are well-known and can be divided into CM- and patient-related factors.

Contrast-Medium-Related Factors

More than 25 years ago, Barrett and Carlisle [1] showed that the incidence of CIN is significantly higher after the administration of high-osmolarity CM (HOCM, osmolality > 1,500 mOsm/kg) than after low-osmolarity CM (LOCM, osmolality < 915 mOsm/kg). Today, it is recommended to avoid the use of HOCM in patients at increased risk of CIN.

Are there differences in nephrotoxicity among the other available CM, either LOCM or iso-osmolar CM (IOCM, osmolality always 290 mOSM/kg)? Eight non-ionic monomers (iohexol, iomeprol, iopamidol, iopentol, ioxilan, iopromide, ioversol, iobiditrol), one ionic dimer (ioxaglate), and one non-ionic dimer (iodixanol) are approved for intravascular use (their use varies from country to country). One non-ionic dimer is not approved for intravascular use (iotrolan) and another is under clinical testing (iosimenol).

The appropriateness of grouping all LOCM into one class and considering all of them as equally

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nephrotoxic is heavily debated, as there may be differences in nephrotoxic potential between the various monomers [2, 3]. No side-by-side comparisons of non-ionic monomers in risk patients, however, are yet available.

Several studies have instead compared LOCM with IOCM, most often following intra-arterial administration of these agents, and a few following their intravenous injection. In 2003, the results of a prospective study (the NEPHRIC study) conducted by Aspelin et al. [4] in 129 patients with moderate chronic kidney disease and diabetes mellitus showed that, compared to iodixanol, the intra-arterial use of iohexol resulted in a significantly higher incidence of CIN. The two groups differed significantly with regard to interventional procedures and length of diabetes, but in other aspects they were comparable. The CIN endpoint was defined as an absolute increase in serum creatinine (SCr) > 44 μmol/l (0.5 mg/dl) within 72 hours. The rate of CIN was 26% of patients receiving iohexol and 4% of those administered iodixanol intra-arterially ($p < 0.001$). Using the same endpoint, Jo et al. [5] did not find significant differences between IOCM iodixanol and a LOCM, the ionic dimer ioxaglate, in 275 patients with chronic kidney disease undergoing coronary procedures. In a retrospective study of 225 patients with moderate-to-severe renal impairment, Briguori et al. [6] could not find differences in the incidence of CIN in patients receiving iodixanol or the LOCM non-ionic monomer iobitridol. In these two latter studies, however, only a proportion of the study patients were diabetic.

Recently, McCullough et al. [7] conducted a pooled analysis using a clinical trial database on iodixanol, maintained by General Electric Healthcare (Waukesha, WI). This pooled analysis included prospective, double-blind, randomized controlled trials that compared iodixanol with LOCM in adult patients undergoing angiographic examinations and reported SCr values at baseline and after CM administration. The vast majority of LOCM (> 89%) patients had received iohexol or ioxaglate; only 5% had received iopamidol [8], and a similar percentage iopromide [9]. The results showed a significant difference in CIN rates between the two groups. Nevertheless, it was difficult to conclude that iodixanol is less nephrotoxic than all other LOCM. For instance, the only study that included iopamidol in the analysis was conducted in patients with normal renal function who underwent femoral angiography, with SCr measured at baseline and at 4 and 18 h post-CM. In that study [8], there was only one case of CIN, following iodixanol. Most of the weight of the analysis was carried by the NEPHRIC study, clearly an outlier among the various studies in the analysis [7]. A similar bias was described by Pannu et al. [10], who assessed the preventative effect of *N*-acetyl-cysteine in a meta-analysis and showed that one study, published by Tepel et al. [11] in the New England Journal of Medicine, carried most of the weight of the final results, showing a positive effect of the anti-oxidant. Tepel et al. [11] found a 2% incidence of CIN when acetylcysteine (600 mg × 2 daily × 2 days) was administered and 21% when acetylcysteine was not given. Both groups received intravenous hydration with half-isotonic saline and only 75 ml iopromide intravenously for CT. In the 14 comparative studies included in the meta-analysis of Pannu et al. [10], the CM was given intra-arterially and at higher doses. The most striking aspect is that both the study of Tepel et al. [11] and the study of Aspelin et al. [4] have had a great impact on the radiological world [12]. The 40–50 studies and more than 15 meta-analyses stimulated by the Tepel study [11] have been of varying quality [13]. It is difficult to find two outlier studies so influential for daily routine practice. Thomsen and Morcos [12] analyzed the various guidelines and found that, in principle, there was nothing new compared with the 1999 guidelines from the European Society of Urogenital Radiology (ESUR) [14] and concluded that evidence for using iodixanol and acetylcysteine following the intra-arterial administration of CM is lacking. As a matter of fact, the two first authors (M Tepel and P Aspelin) of those outlier studies recently published a review paper [15] and concluded that "prospective, randomized trials... significant differences between contrast agents due to their physicochemical properties, and low-osmolar or iso-osmolar contrast media should be used to prevent contrast medium induced nephropathy in at-risk patients" and that there is limited evidence that any pharmaceutical intervention, e.g., acetylcysteine, can prevent CIN.

Regardless of the controversy about potential differences in nephrotoxicity between IOCM and LOCM following their intra-arterial administration, it is clear that there is no difference at all following their intravenous injection. In a randomized, multicenter trial (the IMPACT study), Barrett et al. [16], using the same endpoint as Aspelin et al. in the NEPHRIC study [4], recently showed a 2.6% incidence of CIN after intravenous injection of iodixanol for CT and 0% after injection of iopamidol. All patients had reduced renal function even though the hydration regimen was left to the local centers (only ~65% of the patients received volume supple-

mentation). The results of the IMPACT study confirmed the conclusions of previous, smaller studies by Carraro et al. [17] and Kolehmainen et al. [18], neither of which found any difference between iodixanol and the non-ionic LOCM iopromide and iobiditrol, respectively, in patients with chronic kidney disease. Differences in nephrotoxicity due to iodixanol vs. non-ionic monomers were found in a comparison of the dimer with iohexol, which led Bettmann [2], Sharma & Kini [19], and Solomon and DuMouchel [3] to speculate that the nephrotoxic potential of the various non-ionic monomers and iohexol differs. Solomon and DuMouchel [3] conducted a systematic analysis of published papers and FDA reports of adverse events; they found that the risk of CIN was higher in patients administered iohexol than those receiving the non-ionic monomer iopamidol. Bettmann [2] and Sharma & Kini [18] analyzed arms of controlled studies of patients with chronic kidney disease who received no pre-medication and showed that the average incidence of CIN after iopamidol was significantly lower than after iohexol, whereas the incidence after iodixanol varied from 3 to 33%.

Thus, it cannot be excluded that there are differences in the nephrotoxic potentials of the various LOCM. It seems inappropriate to group all non-ionic monomers together in any review or meta-analysis. Clearly, the nephrotoxicity of iohexol cannot be considered representative of that of the other non-ionic monomers. The different aspects of these CMs have been overlooked in the past. Only side-by-side randomized, double-blind comparisons of iohexol with other non-ionic monomers will be able to confirm a greater nephrotoxicity of iohexol. Today, only limited conclusions can be drawn: (a) the NEPHRIC study showed that iodixanol is less nephrotoxic than iohexol following intra-arterial injection; (b) iodixanol is not less nephrotoxic than other non-ionic monomers following their intra-arterial or intravenous administration; (c) when the osmolality of CM solutions is below 1,000 mOsm/kg, osmolality does not play a significant role in the pathogenesis of CIN.

It has been proposed that gadolinium based CM should be used in patients with increased risk of CIN. This proposal was based on the study of Prince et al. [20], who assessed the increase in SCr after enhanced MRI and CECT in 64 patients undergoing both examinations on separate days. Increased SCr was found only after CT with an iodine-based contrast agent. However, Sam et al. [21] showed in a retrospective analysis that the incidence of CM-induced nephropathy (defined as anuria) after intravenous administration was 1.9% and after intra-arterial administration 9.5%. Dialysis was necessary in 40% of those developing anuria. However, the average dose of the gadolinium-based contrast agent was three fold or slightly higher in that study. Prince et al. [20] used the standard dose. Thomsen [22] reported a patient with diabetic nephropathy who developed anuria after 0.14 mmol gadodiamide/kg but not 2 years earlier after 120 ml of 350 mg iohexol/ml.

Patient-Related Factors

Reduced renal function is the most important risk factor for CIN [23] – poorer renal function (glomerular filtration rate, GFR) means higher risk [24]. Therefore, it is crucial to identify those patients with reduced renal function. Several studies have shown that it is not cost-effective to measure SCr and estimate the GFR in all patients [25]. As a matter of fact, formulas like those proposed by Cockroft-Gault [26] and the Modification of Diet in Renal Disease (MDRD) study [27] are only useful in patients with reduced renal function (< 60 ml/min). The Contrast Media Safety Committee of the European Society of Urogenital Radiology recommended that SCr is measured and estimated GFR (eGFR) calculated in patients: (1) with previously raised SCr, (2) taking metformin, (3) who will receive intra-arterial contrast medium, and (4) who have a history that raises suspicion of increased SCr (renal disease, renal surgery, proteinuria, diabetes mellitus, hypertension, gout and recent intake of nephrotoxic drugs) [25]. In patients with abnormal Scr/eGFR, the committee recommended the use of: (1) low-or iso-osmolar contrast media, (2) stopping administration of nephrotoxic drugs for at least 24 h, and (3) considering alternative imaging techniques that do not require the administration of iodinated CM [14, 23]. It is very important that the patient is well-hydrated; a minimum of 100 ml (e.g., soft drinks or, intravenously, normal saline, depending on the clinical situation) should be given per hour starting 4 h before and continuing 24 h after CM administration.

Acute Non-renal Adverse Reactions

The incidence of acute non-renal adverse reactions requiring acute treatment significantly decreased after the introduction of LOCM and IOCM [28]. Consequently, most radiologists are no longer adequately prepared to treat acute non-renal adverse reactions. In moderate or severe acute adverse reactions, instant

treatment is often mandatory [29]. Although the venous access used to administer the CM may no longer be present, the treatment procedure must be instituted.

Acute non-renal adverse reactions may be mild (nausea, vomiting, urticaria, itching), moderate (severe vomiting, marked urticaria, bronchospasm, facial/laryngeal edema, vasovagal attack), or severe (hypotensive shock, respiratory arrest, cardiac arrest, convulsion). Patients at risk of adverse reactions are those who previously have had a moderate or severe reaction to an iodine or gadolinium agent and those with asthma and/or allergy requiring medical treatment [30]. In the era of HOCMs, the administration of steroids was recommended as a pre-treatment in patients with increased risk of acute non-renal reactions. There is no evidence that steroids are useful in the era of LOCM and IOCM [30]. It is certain that no form of prophylaxis can avoid the occurrence of acute non-renal reactions; therefore, it is important that the radiologist be prepared to treat post-CM reactions. First-line drugs and equipment should be readily available in rooms where CM is injected. Simple instructions should be readily available, and a limited number of drugs should be administered to avoid mistakes. The ESUR Contrast Media Safety Committee recommended that the following first-line emergency drugs and instruments are available in the examination room: oxygen, adrenaline 1:1,000, antihistamine H1 (suitable for injection), atropine, β2-agonist metered dose inhaler, I.V. fluids (normal saline or Ringer's solution), anti-convulsive drugs (diazepam), sphygmomanometer, and a one-way mouth "breather" apparatus [29]. The radiologist should remain nearby for at least the first critical minutes following contrast injection and should remain in the immediate vicinity for the next 30–45 min. If there is an increased risk of an adverse reaction, venous access should be left in place. Simple instructions about how to handle the various reactions as well as a form to report the episode should be on hand and readily accesible.

Important first-line management includes establishment of an adequate airway, oxygen supplementation, administration of intravascular physiological fluids, and measuring the patient's blood pressure and heart rate [29]. Talking to the patient as his or her pulse rate is checked provides useful initial information to the radiologist: breathing is assessed, the possibility of a vagal reaction (bradycardia) is determined, and a rough estimate of systolic pressure is obtained (a palpable radial artery pulse approximates a systolic pressure of 80–90 mmHg).

Late Reactions

Late adverse reactions are those that occur 1 h to 1 week after CM injection (delayed reaction) or more than 1 week after CM injection (very-late reaction).

Delayed reactions, particularly skin rash, are seen following the administration of iodinated CM [30]. The incidence is higher after IOCM than after non-ionic LOCMs [31]. Patients at risk are those who have had a previous CM reaction and those who are treated with interleukin-2. There is no evidence based way of protecting the patient from a delayed reaction, and treatment is symptomatic. Involvement of a doctor is rarely necessary. Currently, no delayed adverse reactions after gadolinium-based contrast agents are known.

Very Late Reactions

Iodine-Based Contrast Agents

Thyrotoxicosis may occur after the administration of iodine-based CM [32]. As a matter of fact, it is contraindicated to administer these agents to patients with manifest hyperthyroidism. Patients at risk are those with Grave's disease, multinodular goiter, or thyroid autonomy, especially if they are elderly and/or live in an area of dietary iodine deficiency. Iodinated CM should not be given to patients with manifest hyperthyroidism. Although prophylaxis is generally not necessary [30], in selected high-risk patients, prophylactic treatment may be given by an endocrinologist; this is more relevant in areas of dietary iodine deficiency. After the injection of iodinated CM, patients at risk should be closely monitored by an endocrinologist. Intravenous cholangiographic CM should not be given to patients at risk.

Gadolinium-Based Contrast Agents

It has been proposed that gadolinium-based contrast agents should be used instead of iodine-based ones for radiography of patients at increased risk of CIN, even though there is no evidence that gadolinium-based agents are less nephrotoxic than iodine-based contrast agents, when administered in equimolar doses [33]. However, the extracellular non-ionic gadolinium-based LOCM gadodiamide may trigger the development of nephrogenic systemic fibrosis up to several weeks after its administration in patients

with end-stage renal failure or those who are on dialysis [34, 35, 36] (the same patient group that has an increased risk of CIN). Nephrogenic systemic fibrosis was recognized in 1997 in California [37]. The typical patient is middle-aged and has end-stage renal disease [38]. Most patients, but not all, are on regular dialysis treatment. The typical course begins with subacute swelling of distal parts of the extremities and is followed in subsequent weeks by severe skin induration and sometimes anatomical extension to involve the thighs, antebrachium, and lower abdomen. The skin induration may be aggressive and associated with constant pain, muscle restlessness, and loss of skin flexibility. In some cases, nephrogenic systemic fibrosis leads to serious physical disability, including the patient's need for a wheelchair. Nephrogenic systemic fibrosis was initially observed in and thought to solely affect the skin – it was initially called nephrogenic fibrosing dermopathy – but it is now known that several organs, including the liver, lungs, muscles, and heart, may be involved. Organ involvement may explain the suspected increased mortality in patients with nephrogenic systemic fibrosis [38].

Several of the patients with nephrogenic systemic fibrosis described by Marckmann [35] had been previously exposed to gadodiamide without developing signs of the disease. This observation suggests that gadodiamide is a necessary, but not sufficient cause of nephrogenic systemic fibrosis. Certain other, as-yet-unidentified factors were therefore suggested to play a role. in the pathogenesis of this disease.

Whether other gadolinium-based contrast agents can trigger the development of nephrogenic systemic fibrosis is not yet clear. As of December 2006, there were no published/peer-reviewed reports. Careful analyses of the available data and further research are strongly warranted. It is important that all radiologists are informed about this serious late adverse reaction. Patients with a positive history of exposure to gadolinium-based CM should be reported to the National Medicines Agencies. At this stage, according to the available information, gadodiamide should not be administered to patients with renal impairment, including those on dialysis [34].

Extravasation

Extravasation of CM is a well-recognized complication of contrast-enhanced imaging studies [39]. The use of automated-power fast-flow intravenous injection in MDCT examinations has increased the incidence of extravasation and may result in the release of large volumes of CM in a short period of time, which can cause severe tissue damage. Infants, young children, and unconscious and debilitated patients are particularly at risk. Fortunately, most extravasations are not associated with long-term sequelae. However severe skin necrosis or ulceration may occur. Large volumes (> 50 ml) of HOCM are known to induce significant tissue damage. Compartment syndrome may be associated with the extravasation of large volumes. Conservative management is often adequate but in serious cases the advice of a plastic surgeon is recommended [30].

Conclusion

Administration of CM for MDCT- scanning is generally uncomplicated. However, because complications and adverse reactions may occur, the radiologist should keep the following in mind:

- It is important to determine which patients are at risk of CIN.
- The risk of CIN after intravenous administration of CM is low.
- Differences in the nephrotoxic potentials of the various non-ionic media have not been documented, with one exception: iodixanol may be less nephrotoxic than iohexol.
- Be prepared to treat acute non-renal adverse reactions.
- Iodine agents should not be used in patients with untreated thyrotoxicosis.
- Patients at risk of CIN should not receive gadodiamide.

The decision whether or not to administer a particular CM should not be based on a single report; rather, the evidence should be carefully considered.

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