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Contrast Material and Radiation Exposure

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This chapter reviews the damage done by radiology procedures secondary to injecting contrast material and exposing patients to radiation. The profession of radiology in general, and most radiology departments in particular, go to great lengths to limit this damage. Broadly speaking, the risk from contrast material and radiation exposure on a per procedure basis has decreased through the years, but as the number of procedures keeps increasing the global risk to all patients rises. In addition, for a given individual patient the risk may be significant. The four main points of this chapter are:

1. Contrast induced nephrotoxicity has likely been overestimated and, with current contrast materials, is quite low.
2. Idiopathic hypersensitivity reactions to contrast are rare and require rapid recognition and treatment.
3. Gadolinium-containing (MR) contrast should be avoided in patients with renal failure.
4. Radiation exposure has become a significant concern, particularly in young patients undergoing repeated CT scans.

CONTRAST INDUCED NEPHROTOXICITY HAS LIKELY BEEN OVERESTIMATED AND, WITH CURRENT CONTRAST MATERIALS IS QUITE LOW

To evaluate whether administration of contrast material has caused renal damage, it is necessary to have a measurement of renal function. While genuine creatinine clearance may be calculated by administering and then measuring excretion and serum values of inulin, iothalamate, iohexol, or DTPA[1], such measurements are not routinely used. Current clinical measurements, which are proxies of genuine renal function, have problems. Creatinine clearance requires the (generally impractical) collection of urine and represents the upper limit of the glomerular filtration rate (GFR) rather than GFR itself[1]. Serum creatinine, the most widely used measure of "function", varies between laboratories (by as much as .3 mg/dL) [1] and may increase after eating a large amount of protein (by as much as .2 mg/dL)[2]. It also varies with weight, age, and sex. In addition, small changes of serum creatinine (particularly when the creatinine is low, for example within the normal range) imply large amounts of damage[1]. Furthermore, changes in creatinine may lag behind renal damage by several hours or even days[1]. Thus, the significance of a serum creatinine value of 1.3 in a young, slender woman who had a creatinine of 1.1 yesterday is completely different than a creatinine of 1.3 in an elderly obese man who has had the same value for three years.

One method of compensating for some of the shortcomings of serum creatinine as a measurement of renal function is to *estimate* the glomerular filtration rate (eGFR). This may be done by means of the widely used Cockcroft-Gault or MDRD (Modification of Diet in Renal Disease Study) equations, which take into account age, gender, and body size. However, these equations are only valid if the serum creatinine is stable. Furthermore, in evaluation of acute renal disease, since age, gender, and body size will not change acutely, eGFR will simply reflect changes of serum creatinine anyway[2]. While serum biomarkers (e.g., cystatin C) show promise, none are in current clinical use[3].

Despite the difficulties of measurement of renal function, radiologists still must take renal function into account when administering contrast material. Radiology contrast material has undergone tremendous evolution in the past 50 years, as drug companies competed (and continue to compete) to bring less toxic products to the marketplace (see Table). The ionic, high osmolar contrast materials (HOCM) of yesteryear have largely been supplanted (in all but niche uses), at least in the United States, by nonionic, low osmolar contrast materials (LOCM). The latest product is an iso-osmolar contrast (IOCM). Claims about the relative nephrotoxicity of these different substances (many times driven by marketing) are sometimes conflicting and confusing.

Adding to the confusion is a recent set of articles which indicate that the risk of contrast induced nephrotoxicity may be overstated. Rao and Newhouse[4] reviewed over 3,000 articles regarding contrast induced nephrotoxicity and found only 40 dealing with intravenous injection of contrast material; only two of these contained a control group (not injected with contrast material), and these two studies found no difference (with respect to acute kidney injury) in the injected and non-injected patients. In a subsequent publication, Newhouse et al[5] reviewed the records of over 32,000 hospitalized patients who did not have contrast material but who did have sequential serum creatinine measurements taken, and found substantial variation (both increases and decreases) of serum creatinine measurements through time. The extent of these changes would have led to many of these patients being classified as suffering from "contrast induced nephrotoxicity", (as defined in published literature) had they been given contrast. A subsequent publication by Bruce et al[6] compared three groups: a control group, patients receiving LOCM, and patients receiving IOCM. At least with serum creatinine concentrations below 1.8 mg/dL the incidence of acute kidney injury was similar between the three groups. With higher serum creatinine, there was a difference between the particular LOCM used in this study (Iohexol) and the control group (with a small but statistically significant increase in serum creatinine in the LOCM group), but not between the IOCM (Iodixanol) and the control group.

So is the key to CIN the use of LOCM versus IOCM, with IOCM as safe as saline? Perhaps not: two large, randomized, multi-continent studies known as the IMPACT[7] and the PREDICT[8] study found no difference between another LOCM (Iopamidol, rather than Iohexol) and an IOCM (Iodixanol) in the rates of CIN in patients with elevated creatinine (IMPACT) and elevated serum creatinine and diabetes (an independent risk factor for CIN) (PREDICT). A meta-analysis by Heinrich et al[9] stated "Iodixanol [IOCM] is not associated with a significantly reduced risk of CIN compared with the LOCM together".

Ellis and Cohan offer an excellent summary of these issues in a "Perspective" article published in the AJR[2]. They note that given the frankly conflicting published results, opinion varies not only regarding the likelihood of CIN but also regarding prevention and treatment of CIN; indeed the recommendations offered by Ellis and Cohan are different than those offered by Rudnick and Tumlin in UpToDate[10].

Recognizing that this is an evolving topic, it should be noted that there is little controversy regarding the administration of LOCM in patients with normal renal function: it is assumed that these patients are at very low risk for CIN and no preventive measures need to be taken. In patients with elevated serum creatinine, radiology departments vary. Most will routinely evaluate serum creatinine, particularly above a cut-off patient age, to identify those who may be at risk for CIN. For those with an elevated creatinine (somewhat arbitrary), one alternative is to offer hydration (IV is

better than oral) with either normal saline or bicarbonate prior to and following the procedure. The (relatively benign, cheap, over-the-counter) antioxidant/mucolytic agent N-acetylcystine may also be administered prior to and following the procedure. The necessity and efficacy of these interventions remains controversial.

How does this knowledge help the primary care provider? You may want to check out how your radiology provider(s) deals with this situation, and confirm that they routinely use either LOCM or IOCM. In addition, you may inquire as to whether they routinely screen for renal insufficiency by checking serum creatinine, and whether they routinely pre-treat patients with an elevated creatinine with either hydration and/or N-acetylcystine. This knowledge may also help you when a radiologist (or radiology technologist) calls to ask you what to do because your patient, scheduled to undergo a radiology test which is usually performed with intravenous contrast, has an elevated creatinine. In patients who you know have elevated creatinine, you may wish to review with the radiologist the necessity of injecting contrast and review other diagnostic possibilities (noncontrast CT, ultrasound, noncontrast MR[1], and nuclear medicine options) to obtain the necessary diagnostic information. Finally, in patients who develop what appears to be CIN following contrast injection, it is reasonable to search the patient's history for possible alternative causes of acute kidney injury (either prerenal or acute tubular necrosis (ATN)) given the recent information about the relatively low likelihood of CIN. In those patients who have genuine CIN, it is usually a transient and short lived event: return to normal renal function is generally faster than with other causes of ATN.

[1] This list does *not* include contrast-enhanced MR, because the downside of injecting gadolinium based MR contrast (nephrogenic systemic fibrosis) is *far worse* than CIN.

Generic Name	Brand Name
Ionic, monomeric, hyperosmolal (>1400 mosmol/kg)	
Sodium iothalamate	Conray
Sodium diatrizoate	Isopaque
Ionic, dimeric, low-osmolal (600 mosmol/kg)	
Ioxaglate	Hexabrix
Non-ionic, monomeric, low osmolal (500 – 850 mosmol/kg)	
Iohexol	Omnipaque
Iopamidol	Niopan; Isovue
Ioversol	Optiray
Iopromide	Ultravist
Ioxilan	Oxilan
Non-ionic, dimeric, iso-osmolal (290 mosmol/kg)	
Iodixanol	Visipaque

Table. Contrast agents. The agents listed at the top of the table are older, higher osmolal and no longer routinely used in most radiology departments, having been replaced by low osmolal or iso-osmolal agents listed at the bottom of the table.

IDIOPATHIC HYPERSENSITIVITY REACTIONS TO CONTRAST MATERIAL ARE RARE AND REQUIRE RAPID RECOGNITION AND TREATMENT

Reactions to contrast material may be categorized as idiosyncratic hypersensitivity reactions (IHRs) and chemotoxic reactions[11]. Chemotoxic reactions include vasovagal responses, seizures, arrhythmias, and CIN (see above). These will not be discussed further.

IHRs manifest as pruritis, urticaria, angioedema, laryngospasm, bronchospasm, and hypotension and vary from mild (less than 10% with LOCM) to fatal (somewhere between 1:10,000 and 1:100,000). These reactions should be recognized immediately by whoever injects the patient with the contrast material. Treatment for contrast reactions should be done in the radiology department at the time of the reaction by personnel from the radiology

department, the emergency department, or the code team. Primary care practitioners will rarely participate in these events. Treatment is as for other hypersensitivity reactions, with reassurance and antihistamines for mild reactions and more drastic measures (including, but not limited to, IV fluids, oxygen, epinephrine, IV steroids, and pressors) for severe reactions. While the primary care provider may never witness or treat an IHR, the issue may arise for the primary care provider in two scenarios: patients with prior contrast reactions, and patients with asthma/atopy. In patients who have a "history of allergy to contrast material" it is important to first determine the exact nature of the "allergy". If the patient has had an obvious anaphylactic reaction requiring intubation, treatment with epinephrine, cardioversion, or hospitalization, it is best to completely avoid ever again using the specific instigating contrast. Whether an alternative contrast material should be given requires careful consideration and definite precautionary pretreatment, generally with oral steroids and antihistamines divided into several doses the day prior to and the day of the exam. If the patient has had a flushed sensation or nausea and vomiting in response to contrast injection, these are more likely a chemotoxic reaction rather than an idiopathic hypersensitivity reaction and do not place the patient at any additional risk for an IHR. Of course, this leaves a large group of patients that have had minor IHRs in the past with some sneezing or a few hives and itching. The approach to these patients varies from never administering contrast, to completely ignoring the event, and everything in between (including switching contrast and/or pretreatment with steroids and antihistamines), and there is no true consensus as to which is the correct approach.

The other scenario, patients with asthma/atopy, is less confusing: while these patients do bear some additional risk of an IHR (perhaps up to five times for asthmatics), no pre-treatment is generally recommended[11]. Such patients should be given LOCM or IOCM, but this is the nearly universal routine practice now anyway. Incidentally, despite the widespread misconception, a previous reaction to fish or shellfish is *not* an additional or independent risk factor for IHR, fatal or otherwise, from contrast injection, beyond the mild increased risk for anyone with allergies or asthma in general[12].

GADOLINIUM-CONTAINING CONTRAST SHOULD BE AVOIDED IN PATIENTS WITH RENAL FAILURE

What a difference a decade makes! A bit more than ten years ago, intravenous MR contrast compounds containing gadolinium were thought to be almost completely benign when administered in routine doses, and, indeed, were looked upon as a godsend for evaluation of the arterial tree and kidneys in patients with renal failure when there was a need to avoid iodinated contrast because of concerns about CIN (see above). We have progressed from the first case reports regarding nephrogenic systemic fibrosis (NSF) to the point where tort attorneys troll for cases on television in less than fifteen years.

What is NSF? It is a nasty disease consisting of thickening and hardening of the skin with expansion and fibrosis of the dermis that occurs *only* in patients with renal failure[13]. Almost all of these patients have been injected with one of the gadolinium containing MR contrast agents. Conversely, between 2.5% and 5.0% of those patients with renal failure (dialysis patients) will develop NSF. Since there is no way of predicting whether a given renal failure patient will or will not develop NSF (even though 2.5 – 5.0% do), and given the dreadful nature of the disease, there are very few circumstances where it makes sense to use gadolinium based contrast material in these patients. In those cases where it is deemed absolutely necessary to do so, use of gadoteridol (one of the many formulations of gadolinium possible) in the lowest dose, followed immediately by dialysis, is recommended[13].

For patients with an abnormal eGFR who are not in renal failure, there is no consensus regarding what to do, although the risk of NSF seems to be orders of magnitude lower for patients with an eGFR of greater than 30 mL/min compared to those in renal failure. There is probably little if any risk in patients with an eGFR of greater than 60 mL/min.

RADIATION EXPOSURE HAS BECOME A SIGNIFICANT CONCERN FOR CT STUDIES

The average amount of radiation exposure to the United States' population doubled between the early 1980s and 2006, due largely to increased use of radiology services, particularly the increase of CT scans from around 3 million in the early 1980s to 67 million in 2006[14]. Because of the ionizing effect of radiation, exposure to radiation increases the risk of cancer in the exposed patient, and some of these cancers may be lethal. Diagnostic radiology studies (unlike therapeutic radiation) almost never use enough radiation to cause direct effects such as hair loss or skin damage. One way of expressing the risk of radiology procedures is as the increased chance of a death caused by a cancer that has resulted from the radiation exposure. Note that the chance of death from cancer for a given patient with *no* exposure to radiation is, on average, 42%, or 420 per 1,000, and that radiation exposure adds to this risk[15]. Note also that there is no way to tell if a given cancer has developed secondary to administered radiation or some other cause.

So how is radiation measured, and how much does a patient receive during radiology procedures? There are a number of terms that may be used when measuring radiation exposure, but for our purposes we will use milisieverts (mSv). For the energy of radiation used in diagnostic imaging, 1 rad (radiation absorbed dose) = 10 miligray (another radiation absorbed dose) = 1 rem (roentgen-equivalent man) = 10 mSv[16]. Radiation doses vary with the type of procedure and the type of scanner[17]. Ultrasound and MR, of course, do not use ionizing radiation and the risk of death from cancer from use of these modalities is nil. As examples of radiation doses, chest radiographs and extremity radiographs generally result in *minimal* exposure (<0.1 mSv), pelvis radiographs and mammography in *low* exposures (0.1 to 1.0 mSv), single-pass abdominal CT and bone scans in *medium* exposure (1.0 to 10.0 mSv), and multiple-pass CT and whole-body PET in *high* exposure (>10 mSv). To relate the degree of radiation exposure to the likelihood of death from cancer caused by that radiation, it is necessary to extrapolate from data on atomic bomb survivors. In general, the known, *proven* risk increases linearly from doses of about 100 mSv upward, and risks below this level are based on a "linear, no-threshold hypothesis" that lower doses result in less additional cancer risk all the way down to zero radiation dose resulting in zero additional risk[18]. Compared to an adult of age 40, a child is 3-4 times *more* likely to develop a lethal cancer and an 80 year old 3-4 times *less* likely to develop a lethal cancer[15]. *As a generalization* (appropriate to within an order of magnitude): the *additional* risk (added to the background rate 420 cases per 1,000) of developing a lethal cancer from radiation exposure is approximately 1 per 1,000 per 10 mSv. Note that some experts[19] discourage discussing specific numbers with patients, preferring to use the terms "negligible" (<0.1 mSv), "minimal or extremely low" (0.1 – 1.0), "very low" (10-100 mSv), "low" (10 – 100 mSv) and "moderate" (> 100 mSv) to express the *risk* (not the radiation amount) when discussing the topic. For most radiology procedures (with the exception of multi-pass CT), the additional risk of developing a lethal cancer is less than 1 in 1,000. CT manufacturers are presently working diligently to reduce radiation doses, particularly in pediatric populations.

For pregnant patients, note that the risk of developing a lethal cancer within the fetus is less than that for a small child[20], and that there is no evidence of risk for fetal anomalies, intellectual disability, growth restriction, or pregnancy loss for doses less than 50 mSv. For higher doses, during the first 14 days of pregnancy there is an "all-or-none" phenomenon in which the fetus will die or survive without adverse sequelae[21]. During organogenesis (4 to 10 weeks after the last menstrual period), intrauterine growth restriction and congenital malformations may be seen (again, with doses of greater than 50 mSv). Note that fetal exposure (as opposed to maternal exposure) may be negligible in examination of maternal body areas other than the abdomen and pelvis. In general, ionizing radiation is to be avoided during pregnancy with alternative methods of diagnosis (e.g., US) preferred.

An excellent short review on this topic for both primary care practitioners and patients may be found at www.radiologyinfo.org under the tab "safety."

SUMMARY

Contrast induced nephrotoxicity has likely been overestimated and, with the current generation of contrast materials, is quite low. Idiopathic hypersensitivity reactions to contrast are rare but require rapid recognition and treatment. Gadolinium-containing (MR) contrast should be avoided in patients with renal failure. Radiation exposure, particularly with repeated CT scans performed in children, has become a significant concern.

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