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Contrast controversies and confusion

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Abstract

Misunderstandings of the risks of contrast agents have led to the persistence of outdated, non-evidence based policies that are often overly restrictive. This review presents a series of questions that arise in practice concerning such topics of controversy and confusion in regard to contrast media. For each case, we review the current evidence-based best practices for contrast media administration, based largely on the most recent American College of Radiology Manual on Contrast Media.

Introduction

Various contrast media are used routinely in different modalities of medical imaging. Through their enhanced portrayal of anatomy and pathological processes and resultant greatly improved diagnostic accuracy, contrast agents have been instrumental in establishing imaging as one of the cornerstones of medical diagnosis.

However, despite the clear benefits of contrast agents, misunderstandings of their risks have led to the persistence of various practices and policies that are overly restrictive, often to the detriment of patients. For example, a survey of Society of Uroradiology members in 2011 showed inconsistency concerning the use of corticosteroid prophylaxis [1,2].

Many of these outdated policies are not evidence-based, as in many cases no reliable data has existed until recently as to the true risks or lack thereof of contrast media in different scenarios. Some antiquated policies may have been based on actual research or anecdotal experiences that are no longer relevant. For example, early Iodinated Contrast Media (ICM) was of a different formulation, referred to as high-osmolality contrast media. Currently, low-osmolality or iso-osmolality contrast media is used almost universally for CT imaging and these forms of contrast have been shown to have significantly fewer adverse effects [3]. It is also worth noting that many of the early papers discussing contrast risks were from the cardiology literature and were referring to intra-arterial contrast injections for cardiac angiography. Intravenous administration is believed to carry less risk [4].

This review presents a series of questions that arise in practice, some commonly, and some less so. These questions concern topics of controversy and confusion we have encountered in our practice due either to outdated policies or to inaccurate information and unproven beliefs that persist within the medical community. In some cases, these obsolete conventions have been reinforced by well-meaning radiologists, or other radiology department personnel, who were seeking only to protect patients from harm, but instead may have been depriving them of a more valuable diagnostic test [5]. For each case, we review the current evidence-based (when evidence exists) best practic-

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es for contrast media administration, based largely on the most recent American College of Radiology (ACR) Manual on Contrast Media [6]. The ACR manual is a frequently updated guide that is the premier resource for radiologists or other medical professionals seeking information about contrast media. The manual consolidates all up-to-date scientific research and provides consensus opinions of the members of the ACR Committee on Drugs and Contrast Media.

Note that the scenarios in this review are generally referring to intravenous administration of contrast, and when discussing administration of ICM, we are referring specifically to modern low-osmolality or iso-osmolality contrast media.

Can I administer iodinated contrast agents to patients with impaired renal function?

There has been a long-standing fear of the risk of iodinated Contrast-Induced Nephropathy (CIN) in patients with even mild elevation of serum creatinine level. However, CIN needs to be distinguished from post contrast acute kidney injury, which refers to decrease in renal function within a few days after administration of ICM, which may occur regardless of whether the ICM was the cause of it [4,7].

In the last several years, four large studies have been published that specifically examined the issue of CIN. Although there were minor differences in the results of these studies, all of them demonstrated that for patients with stable estimated Glomerular Filtration Rate (eGFR) of ≥45ml/min/1.73m^2, ICM is not an independent risk factor for CIN [8-11]. For patients with stable GFR between 30 and 44 ml/min/1.73m^2, ICM is rarely,if ever, nephrotoxic [8-11]. Two of the studies demonstrated that for patients with eGFR <30 ml/min/1.73m ICM is an independent risk factor for CIN [10,11].

It has been shown that the use of eGFR rather than serum creatinine levels will increase the number of patients identified as at risk of CIN and decrease the number of patients who are considered to be at low risk [8]. The ACR has based its recommendations on the premise that there is very little evidence that ICM results in CIN in patients with eGFR ≥30ml/min/1.73m^2 [6]. As per the ACR, "any threshold put into practice must be weighed on an individual patient level with the benefits of administering contrast material" [6].

The above discussion applies to patients with stable or chronic renal insufficiency. So what about patients with Acute Kidney Injury (AKI)? To our knowledge, there are no published studies examining the risk of worsening or prolonged renal dysfunction inpatients in AKI after administration of ICM. However, these patients in general are significantly more susceptible to nephrotoxin exposure. Neither serum creatinine nor eGFR are accurate predictors of the risk of developing CIN in patients with AKI since these values tend to change slowly in AKI. Therefore, if ICM must be administered, it has to be done with caution and only if benefits outweigh the risks [6].

Patients that are anuric with end stage renal disease are not at risk for developing CIN. Administration of ICM does not carry any nephrotoxicity risk in this group [12].

Can I administer gadolinium contrast agents to patients with impaired renal function?

Unlike ICM, the concern regarding the administration of Gadolinium Based Contrast Agents (GBCA) at clinical doses to patients with impaired renal function is not the danger of developing CIN, but rather the risk of developing Nephrogenic Systemic Fibrosis (NSF). NSF is a rare but potentially very serious systemic condition that is characterized by fibrosis of the skin and other tissues throughout the body [13].

GBCA are divided into three groups based on their association with NSF (Table 1). The strongest association with developing NSF has been shown in patients with eGFR of <30 after administration of Group I agents. The risk of NSF in these patients ranges between 1%-7% [14-16]. Studies have also shown AKI to be an independent risk factor for developing NSF. Close to 20% of reported NSF cases have occurred in patients with AKI [17].

Multiple studies have demonstrated that Group II GBCA have either very low or possibly nonexistent risk of developing NSF. Group III agents are relatively new; therefore, no large studies have examined the risk of developing NSF after administration of these agents.

ACR guidelines dictate that for Group I and III agents, patients on dialysis, with eGFR of <30 ml/min/1.73m^2, or patients in AKI should be considered at risk of developing NSF. Therefore, due to concern for undiagnosed AKI, all in patients receiving either Group I or III GBCA should have an eGFR obtained within two days prior to contrast administration. Patients should also be assessed clinically for AKI as eGFR and creatinine have limited accuracy for detection of AKI. For outpatients receiving Group I or III agents the guidelines state that patients should be screened for renal insufficiency and if there are no risk factors obtaining eGFR is not necessary [6]. Assessment for renal function is not necessary with group II agents given either low or possibly nonexistent risk of developing NSF.

Do I need to check eGFR for all patients prior to administration of contrast agents?

Labs are not mandatory for young patients without any history of renal disease or significant medical problems. This is especially useful in the emergency setting where a delay in imaging may be deleterious to patients. Risk factors that may warrant eGFR assessment include: patients over 60 years of age, history of renal disease (renal transplant, single kidney, renal cancer or surgery), history of hypertension requiring medical therapy, and diabetes mellitus [6].

For patients with end stage renal disease do I need to schedule hemodialysis within 24 hours?

There is a popular notion that patients on hemodialysis must be dialyzed within 24 hours after receiving ICM. There are several reasons this has been a longstanding belief. Firstly, it has been theorized that an oliguric patient can potentially become anuric following ICM administration; however, no published data supports this claim. The other potential concern is that since patients with advanced renal failure are unable to clear excess intravascular volume, the osmotic load from the administration of ICM might precipitate pulmonary edema. This concern may have been valid with previously used high-osmolality contrast agents but is not the case with nonionic contrast agents with low osmolality [12]. Unless a large volume of ICM is administered or the patient has a significant cardiac dysfunction, there is no need for urgent dialysis after ICM administration [6,12].

However, ACR Committee recommendations differ slightly for GBCA. The ACR manual states that if GBCA must be used in patients on hemodialysis, only Group II agents should be used and prompt post-procedural hemodialysis may reduce the like-

lihood of NSF. Although some experts recommend prolonged dialysis or multiple dialysis sessions to increase the clearance of GBCA, given the low or non-existent risk of NSF with Group II agents, multiple dialysis sessions are not warranted as per the ACR manual [6].

Can I administer another dose of ICM to a patient that received a dose less than 24 hours ago?

There has been a longstanding belief that multiple doses of ICM in a short period (less than 24 hours) increase the risk of CIN [18]. The reasoning behind it was that the half-life of low osmolality contrast agents is 2 hours; therefore, it takes 20 hours to fully clear ICM from the system in a patient with normal renal function [19].

However, the studies that recommended limiting multiple doses did not include control groups. Due to the lack of strong supporting data, ACR does not support withholding ICM and does not limit the overall volume of ICM administered within a 24-hour period. In addition, it is not recommended to obtain creatinine levels between the doses given the slow change of creatinine in patients with AKI [6].

Can I administer contrast to a patient with a shellfish allergy?

The risk of allergic-like reaction to ICM is rare and even lower with GBCA [3,20]. Patients with shellfish or povidone-iodine allergies are not at a greater risk for developing an allergic reaction to ICM than those patients with allergies to other non-iodine related material [21]. A severe allergy to any food may increase the risk of an allergic-like contrast reaction by 2-3 fold. Therefore, it is not the type of allergy that is important to identify, but rather the severity. Premedication should be reserved for people with history of moderate to severe reactions. The single best predictor of an allergic-like contrast reaction is a history of prior reaction to the same class of contrast media [3]. The ACR's current recommendation is that patients should receive premedication for a history of prior moderate to severe allergic reaction to ICM, but not for history of food allergies or non contrast drug allergies. Furthermore, there is no cross reactivity between different classes of contrast media; a prior reaction to GBCA does not predict a reaction to ICM any more than any other food or medicine related allergy [6].

Can I administer ICM to a patient with asthma?

There are no clear guidelines as to when premedication in patients with history of asthma is necessary. Patients with history of asthma are at increased risk for allergic-like contrast reaction [3]. However, as per ACR, "restricting contrast medium use or premedicating solely on the basis of a history of asthma is not recommended" [6]. Patients with active asthma may be at higher risk and premedication should be strongly considered [19].

How do I manage patients on metformin?

The major adverse effect of metformin is development of lactic acidosis in patients at risk. Close to 90% of metformin is excreted renally; any impairment of renal function potentially increases the risk of developing metformin-induced lactic acidosis. ICM is not an independent risk factor of developing this adverse reaction; however, the concern arises in patients that develop post-contrast AKI. The Food and Drug Administration recommends that for patients with eGFR<60ml/min/1.73m^2, metformin be withheld for 48 hours after ICM administration and reevaluating the renal function prior to restarting the medication [22]. ACR is less stringent and recommends stratifying patients into two categories: [6]

- Category I: Patients with no evidence of AKI and eGFR ≥ 30ml/min/1.73m^2: there is no need to discontinue metformin either before or after administration of ICM and there is no need to recheck the renal function.

- Category II: Patients who are known to have AKI or eGFR < 30ml/min/1.73m^2, or are undergoing an arterial catheter study that might result in emboli to the renal arteries: metformin should be held for 48 hours after the procedure and renal function must be reassessed prior to reinstating it.

It is not necessary to discontinue metformin in patients receiving GBCA.

How do I manage patients with thyroid conditions?

Thyroid cancer itself is not a contraindication for administration of ICM. However, administration of an iodine load may complicate the diagnosis and treatment of thyroid cancer utilizing radioactive iodine. The uptake of I-131 decreases by approximately 50% at one week after ICM but normalizes after a few weeks [6]. Iodinated oral contrast should also be avoided since the bowel may absorb a small amount of iodine.

For patients for whom diagnosis or treatment using radioactive iodine is a consideration, ACR recommends a wash-out period of ideally 3-4 weeks in the setting of hyperthyroidism and 6 weeks in hypothyroidism [6,23]. Also, ICM should be avoided in patients with acute thyroid storm as it can precipitate thyrotoxicosis [6].

What about use of contrast agents in sickle cell disease, pheochromocytoma, multiple myeloma, or myasthenia gravis?

Sickle cell disease: There has been a theoretical concern that GBCA may potentiate magnetic alignment of sickle cells and result in a vaso-occlusive crisis. However, no studies have supported this claim. Therefore, ACR does not recommend withholding either GBCA or ICM in patients with sickle cell disease [6].

Pheochromocytoma: High osmolality contrast agents can increase catecholamine levels in the setting of pheochromocytoma [24]. However, no modern-day contrast agents have been shown to increase the risk of hypertensive crisis. ACR does not recommend restricting or premedicating patients with pheochromocytoma prior to administration of either ICM or GBCA [6].

Multiple Myeloma: High osmolality contrast agents can precipitate irreversible renal failure in the setting of multiple myeloma [25]. However, low osmolality contrast has not been demonstrated to carry such a risk. Therefore, there is no need to restrict the use of ICM in these patients [6].

Myasthenia Gravis: There have been mixed results in patients with myasthenia gravis developing myasthenic symptoms after administration of ICM. One paper demonstrated no increase in risk of myasthenic symptoms after administration of ICM, while another demonstrated that up to 6% of patients developed myasthenic exacerbation within 1 day after administration of low osmolality contrast agent [26,27]. Since more studies are necessary to establish the relationship between myasthenia gravis and ICM, ACR suggests that low osmolality contrast medium should be considered a relative contraindication in patients with myasthenia gravis [6].

Can I administer contrast media to a pregnant patient?

ICM has been shown to cross the placenta. However, in vivo animal studies have demonstrated no mutagenic or teratogenic effects of low osmolality contrast agents. There have been no studies of teratogenic effects in pregnant women.

Despite theoretical concerns, there have been no reports of development of fetal hypothyroidism after maternal IV administration of a water-soluble ICM. The rare reports of fetal hypothyroidism occurred after amniofetography, which was used in the past to detect congenital anomalies and which utilized a lipid-soluble contrast agent [28]. Therefore, ACR does not recommend withholding the use of ICM in pregnant or potentially pregnant patients when it is needed for diagnostic purpose [6].

GBCA cross the placenta and have unknown risks of mutagenesis and of NSF from gadolinium accumulation in amniotic fluid. In a retrospective review, Ray et al demonstrated that there may be a small risk of stillbirths in pregnant patients who received GBCA [29]. The control group was pregnant patients that did not receive MRI rather than patients that had MRI without GBCA. Therefore, due to theoretical risks, ACR recommends administering these agents with caution and only if absolutely necessary. Also, agents that are considered to have a lower risk of NSF (group II) should be selected and the lowest possible diagnostic dose should be administered. It is recommended that an informed consent be obtained from the patient after explaining potential risks.

What should I tell my breastfeeding patients prior to administration of contrast material?

For both ICM and GBCA, only a tiny amount is excreted into breast milk: 0.04% for GBCA and 1% for ICM. Out of this miniscule amount the GI tract absorbs less than 1% [19]. The systemic dose from the breast milk is therefore significantly less than the intravascular dose prescribed to an infant obtaining an imaging study requiring IV contrast [6]. There is a possibility that contrast agents may alter the taste of breast milk. Based on the data available, ACR states that it is safe to continue breastfeeding after contrast administration [6,19,30]. The decision to temporarily stop breast-feeding is left up to the mother. She may choose to stop breastfeeding for 12-24 hours. There is no need to stop breastfeeding for a longer period, as both ICM and GBCA are nearly completely cleared from the bloodstream within 24 hours in patients with normal renal function.

What should I tell my patients about gadolinium deposition in the brain?

Multiple studies demonstrate deposition of gadolinium within neuronal tissues and a dose-dependent relationship with cumulative exposures to GBCA. These findings were demonstrated in patients with normal renal function and it has also been shown that the deposition remains in tissues for months to years after the exposure [31,32]. Furthermore, gadolinium deposition has been demonstrated to occur in patients without any intracranial abnormalities and that the deposits can be seen after as few as four doses [33].

There have been no reports of neurotoxicity in patients receiving GBCA and the clinical significance of gadolinium deposition in the brain remains unclear. Additional research is necessary to study the mechanism of the deposition, chelation state of the deposits and theoretical potential toxicity that may vary for different types of contrast. As per ACR, each time a GBCA is considered, the clinician and radiologist must assess the need of contrast agents for the particular study and whether the benefits outweigh the risks [6].

Is ultrasound contrast media safe?

Ultrasound contrast agents consist of micobubbles or microspheres. These are made up of either an outer phospholipid or protein wall with a central inert echogenic gas, which enhances the acoustic ultrasound signal of blood. It generally remains in the bloodstream and does not cross into the interstitium due to it large size.

The adverse event rate of ultrasound contrast media is similar to or less than that of modern CT and MRI contrast agents. Non-cardiac applications in the pediatric population are safe, with side effects uncommon and typically minor [34]. Ultrasound contrast is contraindicated for intra-arterial injection and in patients with previous hypersensitivity reaction to microspheres. No known renal toxicity has been demonstrated in approved doses.

These agents have not been studied well in pregnant women; therefore they should only be used when benefits outweigh the risks. Since the effects of these agents on breast milk is unknown, breastfeeding mothers should temporarily (~24 hours) discard the milk after intravenous ultrasound contrast media is administered [6].

Conclusion

In this review, we have highlighted some of the scenarios for which outdated, non-evidence based policies and beliefs often still persist. Many longstanding concerns about contrast administration have been debunked or may no longer apply with newer contrast agents. While contrast administration is not always appropriate, it is important that radiologists be familiar with current recommendations regarding contrast media and not overly restricts their use.

The ACR Manual on Contrast Media, from which the recommendations in this review are largely derived, is an excellent resource when faced with questions regarding contrast contraindications. Radiology department guidelines should be updated to reflect current recommendations and best serve our patients.

Table

Table 1: ACR Manual for Classification of Gadolinum-Based Agents.

Group I Greatest number of NSF cases	Group II Few, if any, unconfounded cases of NSF	Group III Limited data regarding NSF risk; few, if any unconfounded cases of NSF reported
Gadodiamide (Omniscan) Gadopentetate dimeglumine (Magnevist) Gadoveretamide (OptiMark)	Gadobenate dimeglumine (Multihance) Gadobutrol (Gadavist) Gadoterate acid (Dotarem) Gadoteridol (ProHance)	Gadoxetate disodium (Eovist; Primovist)

Adapted from: *ACR Manual on Contrast Media Version 10.3*. 2017 [6].

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