HealthManagement.org
Promoting Management and Leadership

Volume 17 - Issue 4, 2017 - Cover Story: Risk & Danger

Risks of contrast agent administration

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Outlines the frequency of adverse effects, prevention and management, and focuses on acute reactions which may occur after intravascular injection of contrast agents, the risk of deterioration in renal function after iodine-based agents, and current anxieties about the long-term safety of gadolinium-based agents.

Contrast agents (or contrast media) are compounds, which are given during radiological examinations to increase the diagnostic information obtained from the images. Iodine-based contrast media are widely used during x-ray and computed tomography (CT), and gadolinium-based contrast agents are widely used during magnetic resonance imaging (MRI). There are microbubble agents for ultrasonography, but these are used less often. Examinations using contrast agents are described as ‘enhanced’ and those without contrast agents as ‘unenhanced’. This review will focus on three important areas of risk: acute reactions which may occur after intravascular injection of contrast agents, the risk of deterioration in renal function after iodinebased agents, and current anxieties about the longterm safety of gadolinium-based agents. The frequency of adverse effects, their prevention and management will be considered.

Acute adverse reactions

Acute adverse reactions are defined as reactions occurring within one hour of injection of the contrast agent,

and may occur after iodine-based, gadolinium-based and ultrasound agents. The majority are mild (eg skin redness, urticaria and itching, nausea) and do not need medical treatment. It is important to be aware that not all mild symptoms after contrast agents are caused by the contrast. This has been shown in prospective studies where patients who had unenhanced scans had similar mild adverse effects to patients who received iodine- or gadolinium-based contrast, although the adverse events were less frequent in the patients who had unenhanced scans (Azzouz et al. 2013). Moderate reactions, such as more severe urticaria, bronchospasm and vomiting are less frequent. Severe reactions, which may be anaphylaxis- like and cause hypotension, cardiac arrhythmias or cardiac arrest and respiratory arrest are rare (Clement and Webb 2014). Modern low osmolality non-ionic iodine-based agents were associated with a reaction rate of 3.13% and a risk of severe reactions of 0.04% in a large series of over 300,000 patients (Katayama et al. 1990), with the risk of death estimated to be less than 1 in 170,000 (Katayama et al. 1990). Gadolinium-based agents are associated with a lower risk of acute reactions, approximately 0.05 to 0.33%, with a risk of death in 0.1 to 2.7 per million (Thomsen and Bongartz 2014; Davenport et al. 2013; Prince et al. 2015). Acute adverse events after ultrasound microbubble agents are even rarer (Bertolotto and Oyen 2014). No differences in the incidence of acute adverse reactions have been shown either among the various low osmolality iodine-based agents or among the different gadolinium-based agents.

Some acute adverse reactions are caused by hypersensitivity or chemotoxicity and a minority appear to be true allergic reactions. Patients who have a moderate or severe reaction to contrast media should have blood tests to check for raised tryptase levels after the reaction and skin tests 1 month after the reaction to determine if there is evidence of true allergy (Clement and Webb 2014).

Patients who previously have had a moderate or severe reaction to contrast medium are at increased risk of a further reaction when they are given contrast medium again. Patients with a history of allergy also have an increased risk of reaction. When there is an increased risk of an acute reaction, it is important to consider whether an alternative examination could provide the required diagnostic information. If allergy to contrast medium has been demonstrated, then a different contrast agent to which the patient does not react on skin testing should be chosen for a subsequent administration.

The evidence for the value of premedication before administration of modern low osmolality iodine-based contrast media with steroids or antihistamines, for example, is weak. After premedication acute ‘breakthrough’ reactions, including anaphylactic shock, may still occur (Davenport and Cohan 2017; Freed et al. 2001; Davenport et al. 2009). The use of premedication has therefore decreased over recent years.

Since a moderate or severe acute reaction, although rare, is possible in any patient, it is essential that radiology departments are fully prepared to deal with management of acute reactions. Patients should remain in a medical environment for 30 minutes after contrast medium injection. There should be first-line drugs and equipment available in the examination room so that there are no delays in starting treatment. Radiology department staff need to be trained in the management of acute reactions, including resuscitation, and training should be repeated regularly to keep skills up to date.

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Renal adverse reactions

It has been recognised for many years that in patients with reduced renal function intravascular administration of iodine-based contrast media may be followed by further deterioration in renal function, with the risk being increased if patients are dehydrated (Fähling et al. 2017; Bartels et al. 1954). In most patients the renal function returns to baseline levels over 1 to 3 weeks, but in some it may persist or lead to end-stage renal failure

requiring dialysis. This adverse effect was called contrast-induced nephropathy (CIN), and CIN has been defined as a decrease in renal function (as evidenced by an increase in serum creatinine by more than 25%), which occurs within 3 days of contrast medium administration in the absence of an alternative aetiology (Thomsen et al. 2014).

Over recent years, the use of iodine-based contrast media has increased, and over the same period there have been many publications about CIN occurring both after intra-arterial contrast medium given for angiography, including coronary angiography and intervention, and after intravenous contrast medium used for enhanced CT. It has been stated that CIN is the third most common cause of hospital–acquired renal failure, accounting for about a tenth of cases (Thomsen et al. 2014). However, most of the published studies have been retrospective, with only a few studies being prospective and using control subjects (Rao and Newhouse 2006; Prasad et al. 2016; McDonald et al. 2013). The lack of control subjects meant that all increases in serum creatinine after contrast medium were attributed to the contrast medium, even though it is known that serum creatinine is affected by many other factors, such as illness, hydration, muscle mass, diet and medication.

A recent prospective study which compared renal function after enhanced and unenhanced CT found that changes in kidney function, as measured by estimated glomerular filtration rate (eGFR), were unrelated to whether or not the patient had received contrast medium (Azzouz et al. 2014). A retrospective literature review, which included data from over 12,500 patients, and in which propensity score analysis was used to simulate randomised controlled studies, showed no difference in the risk of kidney injury between patients who had or had not received intravenous contrast medium (McDonald et al. 2014). These and similar studies indicate that the risk of kidney injury caused by intravenous iodine-based contrast media is much lower than the previous literature suggested. Estimates suggest that an eGFR of 30-45 ml/min/kg is associated with a risk of renal injury of 0-5% (Azzouz et al. 2014). (Normal eGFR is 60ml/ min/kg or greater). Intra-arterial iodine-based contrast medium has been considered to be associated with a higher risk to the kidneys than intravenous contrast, because it reaches them at a higher concentration, and because large volumes of contrast are often used. However recent retrospective studies of large numbers of patients have not confirmed this (McDonald et al. 2016; Tong et al. 2016), and further data are needed to clarify the risk. No differences in the rate of renal adverse events have been shown among the various low osmolality iodine-based contrast media (Thomsen et al. 2014). The term post-contrast kidney injury (PC-AKI) has now replaced the term CIN, to remove the suggestion that the contrast medium is the cause of all renal function deterioration after contrast. Deterioration of renal function after gadolinium-based contrast agents is very rare when the agents are given in approved doses (Thomsen et al. 2014).

To reduce the likelihood of PC-AKI, it is important to identify at-risk patients either by serum creatinine measurement and eGFR calculation, or by using standardised questionnaires, which identify evidence suggesting impaired renal function. The key protective measure is to hydrate at-risk patients intravenously both before and after contrast medium. A variety of prophylactic drugs have been tried, but none has been consistently shown to be successful (Thomsen et al. 2014).

Late adverse effects of gadolinium-based contrast agents

Gadolinium ions are toxic and are therefore bound to a chelate in gadolinium contrast agents to prevent adverse effects. There are two types of chelate—linear and macrocyclic. In the macrocyclic chelates the gadolinium ions are more tightly bound than in the linear chelates, with the result that the macrocyclic chelates are more stable, with a lower risk of gadolinium being released from the molecule (Morcos 2014). As has been outlined, gadolinium-based contrast agents have a lower incidence of acute adverse reactions than iodine-based contrast media, and PC-AKI after gadolinium-based agents is very rare. However, over recent years some late adverse effects of gadoliniumbased agents have been recognised. Some patients with reduced renal function who were given the less stable linear agents developed nephrogenic systemic fibrosis (NS F). The onset of NS F was typically days or even months after contrast administration, with the first signs being skin rashes and thickening. Later, patients developed fibrosis of the muscles and internal organs and in a few patients the

condition was fatal. NS F has not been reported since the use of linear agents was stopped in patients with impaired renal function (Thomsen 2016a; 2016b). It has also become apparent that gadolinium may accumulate over time in the bone, skin, liver and brain in patients who have received gadolinium-based contrast a gents (Thomsen 2016c). Larger amounts accumulate after the linear chelates, and the greater the dose, the greater the accumulation. At present, the significance of this retained gadolinium is unclear, but anxiety, particularly about deposition in the brain, has led to suggestions that the use of the linear agents should be discontinued (Runge 2017).

Conclusion

This brief review of some of the more important adverse effects associated with iodine-and gadolinium-based contrast agents indicates that they are generally safe and have a low incidence of significant side effects, particularly compared to some therapeutic drugs. As with all drugs, it is important that contrast agents are only given when there is a good clinical indication, either to make a diagnosis or to direct an interventional procedure. However, the low risks associated with these agents in most clinical circumstances, and the importance of their use to many important diagnoses (eg the detection of liver metastases) mean that a well indicated enhanced examination should rarely be refused. When the patient is considered to be at increased risk of an adverse effect, it is appropriate to consider the possibility of a different diagnostic test, or perhaps an unenhanced scan. With gadolinium-based agents, at risk patients with impaired renal function should not receive linear agents (European Society of Urogenital Radiology 2017).

Acknowledgement

The author is thankful to Dr. Judith A.W. Webb (London, UK) for the fruitful discussions during the preparation of this manuscript.

Key Points

- Contrast media are available for all radiologic modalities (x-ray and CT-scanning, magnetic resonance imaging, and ultrasonography)
- Mild, moderate or severe acute adverse reactions are seen after administration of any contrast agent; an overwhelming majority are mild. Only moderate and severe reactions require treatment; their prevalence is below 0.5%
- Reduction (mainly temporary) in renal function (post contrast–acute kidney insufficiency [PC-AKI]) is found in patients with reduced renal function after administration of iodine-based contrast media
- Gadolinium-based contrast agents have some specific very late reactions due to the toxic gadolinium eg nephrogenic systemic fibrosis, brain accumulation
- One should never deny a patient a well indicated enhanced examination

Published on : Tue, 19 Sep 2017