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### Safe Use of MRI Contrast Agents

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Much attention has recently been focused on the safe use of gadolinium-based contrast agents (GBCAs) in MRI with regards to nephrogenic systemic fibrosis (NSF). In the wake of its discovery and subsequent investigation, many guidelines were created on the subject. Part one of this article reviews what guidelines are, what GBCAs are, and how GBCAs are used in comparison to iodine-based contrast agents (IBCs).

#### What are Guidelines?

A guideline is any document that aims to streamline particular processes according to a set routine. Medical guidelines form part of clinical governance and can potentially be issued by any interested organisation (governmental, professional, institutional or private). Their objective is to standardise medical care, raise the quality of medical care, improve cost-effectiveness and to minimise risk. Guideline development is based on identification, summary and evaluation of the highest quality current evidence.

Some guideline groups have very specific methodologies (e.g. SIGN & NICE), to reliably obtain best evidence using specific literature search strategies and strict evaluation criteria. In other instances, the process by which the evidence informing a guideline has been obtained and evaluated is not explicit. Equally crucial is the methodology used to define the most important questions to be addressed such that evidence regarding all possible options and outcomes are identified.

#### Risk Benefit Ratios

In the area of GBCA use and NSF the regulatory authorities (EMA and FDA) do not issue guidelines but rather provide information in the form of 'Questions & Answers' and regulate through product labeling, though the FDA has had 'Regulatory Alerts' inserted into many guidelines where the use of contrast enhanced MRI is discussed, for example many of the ACR Appropriateness Criteria (see the U.S. National Guideline Clearing House - [www.guideline.gov](http://www.guideline.gov)). Safety is always a relative word and in diagnostic imaging the risks of an investigation for the individual patient must be balanced against their perceived potential for benefit. While MRI has none of the risks of exposure to ionising radiation associated with radiological techniques such as CT it entails other risks, particularly in relation to the strong magnetic fields employed. These risks are predictable and managed by strict operating procedures, training of all staff in MRI safety, the provision of information to patients prior to scanning and importantly, screening questionnaires. These are all designed to eliminate the possibility of patients potentially coming to harm, for example by ensuring that those with MRI incompatible implanted devices are not exposed to a magnetic field.

#### Contrast Agents in MRI

Another potential source of risk in radiological procedures are the adjunctive techniques that may be required to enhance scans. For example, conventional angiography and many CT studies employ injections of intravascular iodinebased contrast media (IBCM). However, through refinement in their chemistry, modern IBCM now have much lower incidences of minor and major reactions compared with those compounds used in years past. GBCAs frequently used in MRI use chelating agents to bind the potentially toxic gadolinium cation in a stable compound that can be injected intravascularly without toxicity for human MR imaging. This chelation binds the gadolinium in a stable form with low toxicity and these agents in general have similar pharmacokinetics to IBCM, being predominantly excreted unchanged in the urine by glomerular filtration. The exceptions are gadobenate dimeglumine (Multihance), gadofosveset trisodium (vasovist) and gadoxetic acid disodium (Primovist/Eovist) which also undergo approximately four, nine and 50 percent hepatobiliary excretion respectively.

#### Safety of GBCA Versus IBCM

GBCAs are associated with similar idiosyncratic and non-idiosyncratic adverse reactions as IBCM. However, the risks of these are orders of magnitude lower in terms of frequency of anaphylaxis and potential for nephropathy than the IBCM, partly through the much lower doses required for GBCA enhancement of MRI scans compared to the volumes of IBCM needed in CT and conventional angiography. For example, whilst commercial GBCAs are more nephrotoxic than IBCM in equimolar amounts, this has not been a significant clinical problem as they are used in much lower doses. Individual case reports of GBCA induced nephropathy at clinical doses in patients with pre-existing renal insufficiency have been published. However, the patients involved had the same risk factors as for CIN with IBCM suggesting similar mechanisms of chemotoxicity rather than anything specific to the gadolinium itself. Rates of adverse events of GBCAs are even lower than for modern IBCM, for example, the rate of fatal, unpredictable idiosyncratic anaphylactic reactions with GBCA use is estimated at approximately 1:100,000 administrations compared to 1:40,000 for IBCM.

#### Studies Prove Usefulness of GBCAs

With MRI, the excellent soft tissue contrasts achievable compared to CT and other modalities led some to believe that exogenously administered contrast would be superfluous. However, research and deployment has validated the clinical usefulness of GBCAs from CNS imaging through to cancer imaging, myocardial perfusion and more. This has led to GBCA use becoming the 'standard of care' for a variety of MRI studies. In vascular imaging early non-contrast enhanced magnetic resonance angiography (MRA) techniques were often hampered (particularly in body imaging) by long acquisition times and artifacts. In this respect the advent of contrast enhanced MRA (CE-MRA) was a real advance as CE-MRA allows repeatable and dynamic non-invasive assessment of the vasculature on an outpatient basis without the need for exposure to ionising radiation and with contrast agents that are less nephrotoxic in the doses required than conventional iodine-based media. This requirement for relatively increased doses in CE-MRA has recently been reduced by advances in MRI hardware (such as dedicated array coils) and software (parallel imaging, time resolved/echo sharing etc.) that have been developed for vascular applications. In patients with renal disease contrast enhanced examinations have been quite widely used as part of the investigation of the cause of renal impairment, especially in evaluating for

potentially correctable renal arterial disease.

In patients with more established renal failure then the diagnosis of the vascular complications of renal disease (such as lower limb ischaemia) is important and furthermore contrast enhanced MR venography (MRv) techniques have proven extremely useful for the assessment of the venous stenoses and thromboses occurring as complications of central venous access for haemodialysis. Indeed, CE-MRv provided exquisite detail of venous disease in these patients in a way difficult to achieve by more conventional means.

Part two of this series on contrast media will appear in the next edition of IMAGING Management.

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