HealthManagement
Promoting Management and Leadership

Volume 10 - Issue 4, 2010 - Patient Safety

Patient Safety & MRI Contrast Agents

NSF Signs & Symptoms

In some patients that go on to develop nephrogenic systemic fibrosis, localised non-progressive skin thickening and induration may be the only manifestation, though this can be particularly problematic if this interferes with dialysis shunt access. In more severe cases skin thickening adjacent to joints can lead to contractures and hence impaired mobility while in the most severe cases (a minority) the disease is relentlessly progressive and can be fatal. As yet there are no effective treatments though regression following improvement in renal function, particularly after transplantation is described and recently there is a report that the use of Imatinib mesilate (Gleevec) can be beneficial.

Newer reports based on larger series with case control analysis have better determined the risk of development of NSF as between 3 - 5 percent of patients in end-stage renal failure on dialysis exposed to GBCAs. These studies have also shown a form of dose-response relationship, i.e. those patients exposed to higher doses or repeat examinations were more likely to develop NSF. However, it should also be noted that of course this means that nearly 97% of these patients on renal replacement therapy do not develop clinical features of NSF, as such this is not clear causation but rather a strong association.

Further work finding of gadolinium retained in the skin biopsy specimens from NSF patients even many months after contrast exposure indicates a role for gadolinium in the pathogenesis of NSF. The transmetallation theory suggests that the gadolinium cation (Gd+++) is exchanged from the GBCA chelate for other cations, perhaps promoted by disturbed acid-base balance along with the very prolonged time that these agents remain in the body in renal failure patients.

How the gadolinium then mediates the development of NSF is not clear but it is thought that circulating fibrocytes migrate to the extravascular space and initiate inappropriate collagen deposition resulting in the clinically manifest disease process. However, clearly the majority of patients in renal failure who have had GBCAs administered have not developed NSF and as yet the other factors that must additionally determine the development of this disease have to be elucidated.

Background to Guideline Creation

This knowledge is important when drawing up guidelines as we can only truly assess risk once causation is fully elucidated, in the meanwhile the following areas have fed into guideline creation:

Renal Failure – Renal failure is a requirement for the manifestation of this condition, but at just what level of renal impairment does the risk become a clinical problem? The vast majority of cases have occurred in patients with stage 5 chronic kidney disease (CKD) – i.e. effectively those at the stage of requiring dialysis or established on dialysis with an estimated glomerular filtration rate (eGFR) of less then 15 ml/min. While there have been a few cases with estimated GFRs greater than this they have all been in the context of acute renal injury where estimation of GFR using the formulae designed for chronic renal disease markedly underestimates the actual degree of renal impairment. Investigations looking into the occurrence of NSF in patients with stable less severe renal disease (CKD stage 3 moderate, eGFR of 30 - 59 ml/min/1.73m2 & CKD stage 4 severe 15 - 29 ml/min/1.73m2 have confirmed that this is a disease limited to those with established renal failure (CKD stage 5) and acute kidney injury scenarios. However, many of the current guidelines were developed before this had become entirely clear, hence the differences in the level of renal impairment thought to be a risk.

Dialysis – Does dialysis in relation to GBCA administration help? Currently the role of immediate post-MRI dialysis is uncertain, while there is little positive evidence that it can help to avert NSF it is theoretically attractive and the current ACR and CAR guidelines recommend its use. However, it is likely this dialysis really does need to be immediate, as NSF has certainly occurred in patients despite same day dialysis post-MRI. This is clearly only practicable where patients already have dialysis access in place prior to the MRI scan. Perhaps equally or more important is to have had the patient adequately dialysed prior to the administration of GBCAs as there certainly seems to be increasing evidence that poor dialysis prior to GBCA enhanced MRI is a risk factor but this has not been addressed in any of the guidelines.

Dose of Contrast Agent – How have guidelines approached the issue of GBCA dose? The doses associated with NSF in the published literature have mainly been in the 0.2 mmol/kg to 0.3 mmol/kg range (i.e. double and triple 'standard' dose) as often used for CE-MRA and cardiac MRI. The rise in NSF incidence does indeed parallel the use of higher doses in cardiac and vascular studies with very few reports of NSF following single/standard dose administration despite many administrations to patients at high risk of the agents most associated with development of NSF. However, the discussions regarding dose in the guidelines were not the most prominent aspects in the guidelines that originally emerged, though more recent updates have focussed more on this issue. Perhaps the most explicit is the statement in the RANZCR document -

- 'Use the minimum diagnostically adequate dose of gadolinium (there is some evidence for a "dose-risk" relationship)'
- The RCR guidelines state - 'Give the lowest dose possible to achieve a diagnostic examination'
- The EMEA states - 'Dose should be restricted to the minimum recommended dose in patients with severe kidney problems'
- ESUR - 'In all patients use the smallest amount of contrast medium necessary for a diagnostic result'
- The latest ACR guidance has this year also suggested using the lowest dose compatible with a diagnostic examination and avoiding high dose in at risk patients.

Which Agents are Linked to NSF?

Whether the various different GBCAs are more or less likely to predispose patients to NSF is another important issue. There is increasing evidence of differences between the available agents, particularly from pre-clinical work but the guidelines tackle this in different ways, partly through geographic concerns. For example the U.S. oriented guidelines deal with a market where there is a more limited choice with fewer cyclic agents available.

The large majority of reported cases have been with gadodiamide with fewer involving gadoversetamide and gadopentate dimeglumine - all linear chelates. There are no severe cases confirmed following sole administration of gadobenate dimeglumine (the linear chelate with the highest stability indices and 3 percent hepatobiliary excretion) and none to date with sole administration of any of the cyclic chelates gadoteridol, gadoterate meglumine or gadobutrol.

If transmetallation is an important step in the pathogenesis of NSF then the more stable agents should be safer. The European and Australasian guidelines took this on board with an approach assigning the ionic linear chelates gadodiamide, gadoversetamide and gadopentate dimeglumine a higher risk profile as compared to the cyclic chelates especially. More recently the ACR guidelines have also adopted an approach in the version 7 revision to their Manual on Contrast Media that divides the agents into three classes according to their association with unconfounded cases of NSF and volume of utlisation. In group 1 gadodiamide, gadoversetamide and gadopentate dimeglumine are recommended not to be used in high risk patients (eGFR < 30, end-stage renal disease on chronic dialysis and acute kidney injury).

The potential for hepatobiliary excretion of some of the agents may be a theoretical advantage for administration in patients with renal failure (but preserved hepatic function). As yet there is no clinical evidence to support this supposition though it is mentioned in the RANZCR document where regarding the factors affecting the choice of agent the following is stated –'Use of agents which have significant biliary excretion, as well as (or instead of) renal excretion. However, there is little reported experience with this strategy'.

Certainly the formulation of the GBCA used appears to be important with the cyclic chelates that have highest stability constants generally deemed to be those with the lowest risk. Whether this issue has been incorporated into the various guidelines relates to the commercial environment in which the specific guidelines operate, specifically whether there is appropriate choice of licensed products.

Other Factors

We know that most patients in renal failure administered GBCAs even in high dose do not develop NSF hence other factors must contribute. However, they have not been elucidated and although there are suspicions regarding erythropoietin treatment, iron levels, phosphate binding therapies etc. none of these other features has been confirmed hence none has entered into any of the guidelines. The type of dialysis does seem to influence risk, in that peritoneal dialysis is the least efficient at clearing exogenously administered compounds and the RANZCR guidance specifically states – 'Avoid all gadolinium-based MRI contrast agents in patients receiving peritoneal dialysis (clearance of the agent in these patients is very slow; in one study, their measured risk of NSF was seven times higher than that of haemodialysis patients)'.
The converse of this question of course is whether there are protective factors against the development of NSF. This would be critically important as if a modifiable factor was found then protection could then be given to allow safer GBCA enhanced MRI studies when required.

Prior Research Essential

In practice, the implications are that those involved in imaging must know more about their patients prior to MRI scanning than has been the case up until now and guidelines help to promote this. For example, knowledge of renal functional status is most useful at the time of scan request prior to scheduling and this requires education of the referrer, more easily achieved with the backing of guidance that is perceived as credible and reflecting best practice from a respected professional body.
Where patients with severe renal impairment are considered for MRI with contrast then a judgment needs to be made as to whether the risks of GBCA use as we currently perceive them outweigh the risks of alternative imaging techniques. In vascular imaging the hazards of conventional arteriography with arterial puncture, ionising radiation and iodinated contrast media. If GBCA are to be used then the lowest dose feasible is currently advocated (such as half usual dose) and here GBCAs with increased specific relaxivity could be advantageous.

Conclusion

GBCAs remain extremely safe for the vast majority of patients and exams. Obviously with the intense research focus our knowledge will continue to evolve. Current guidelines have differences that reflect differing interpretations of the initial knowledge available in this field coloured by the local regulatory and commercial environments specific to the audiences they address though the markets are changing with increasing availability of the more stable linear and cyclic agents.

For example, this helps to explain the fact that until recently there has been less focus on the differences between linear and cyclic chelate GBCAs in the U.S. guidance where the choice of agents is relatively restricted compared to Europe. Thankfully, with the recent ACR guidance changes the U.S. and European guidelines are now much more comparable. The issue of a dose response similarly received little attention until recently and is not seen as a relevant issue in Japan where high dose techniques have traditionally not been used.

Perhaps the most glaring omission from most of the guidelines is a balanced discussion of the relative risks of alternative imaging modalities or the risk of lack of appropriate investigation in order to put the guidance in context since alternative imaging strategies will also entail degrees of risk either directly (e.g. contrast nephropathy, ionising radiation) or indirectly through lower diagnostic accuracy. Obviously, due to their nature the detail of the various guidelines will always lag behind the improving scientific knowledge, hence it is in the interests of all that mechanisms are found to ensure regular update and revision to guidelines as and when new relevant knowledge becomes available.

Published on : Wed, 15 Dec 2010