Contrast Agent Restrictions May Help Curb NSF

VITALS

Findings: No new cases of nephrogenic systemic fibrosis were reported after reduction in use of gadolinium-based contrast agents, as well as substitution of new agents.

Data Source: Patient records at two tertiary care centers.

Disclosure: One study author received research support from GE Healthcare, Bayer Healthcare Pharmaceuticals, and Bracco, makers of gadolinium-based contrast agents used in the study.

BY KERRI WACHTER

No new cases of nephrogenic systemic fibrosis occurred at two large tertiary care facilities after more restrictive policies on the use of gadolinium-based contrast agents were introduced.

Before the changes, the incidence of nephrogenic systemic fibrosis (NSF) was 1 in 33 in high-risk patients. In patients on dialysis, the incidence of NSF was 1 in 35, according Dr. Ersan Altun, a radiologist at the University of North Carolina in Chapel Hill, and his coauthors.

"The absence of NSF cases in the postadoption period may reflect the effect of the use of different GBCAs [gadolinium-based contrast agents] and the adoption of restrictive GBCA policies on the incidence of NSF," they wrote (Radiology 2009;253:689-96).

Gadolinium-based contrast agents vary in their dissociation rates, and dissociation of the gadolinium ion from the chelating ligand may be a risk factor for NSF.

In 2006, reports to the Food and Drug Administration suggested a strong association between NSF and gadolinium-based contrast agents used in MRI. The exact mechanism remains unknown; however, GBCAs vary in their dissociation rates, and dissociation of the gadolinium ion from the chelating ligand may be a risk factor for NSF, the researchers said.

Cases of NSF were documented at two tertiary care centers for three periods: before the adoption of restrictive GBCA policies and a change in agents, during the transition period, and after the adoption of these policieschanges.

The new policies included careful screening of patients for risk factors for NSF such as renal disease, hypertension, dialysis, and diabetes before they underwent gadolinium-enhanced MRI. If GBCA-enhanced imaging was unavoidable in a patient deemed to be at high risk, a half dose of gadobenate dimeglumine was used. The policies also specified greater use of other types of imaging that don't require contrast agents.

In addition, gadolinium-enhanced MRI was not performed in pregnant women unless maternal survival was at stake, was not performed in any patient twice within 48 hours unless absolutely necessary, and was not done twice within 48 hours in any patient deemed to be at high risk of NSF.

Before the adoption of the changes, both of the centers used gadodiamide (Omniscan, GE Healthcare). After the adoption of revised policies, both centers used either gadobenate dimeglumine (Multihance, Bracco Diagnostics) or gadopentetate dimeglumine (Magnevist, Bayer Healthcare Pharmaceuticals). Gadobenate was used for all MRI studies of adults, patients younger than 1 year, and pediatric patients at risk for the development of NSF. Gadopentetate was used for pediatric patients 1 year and older who were not at risk for NSF. Both of the agents have lower dissociation rates than gadodiamide.

Patients considered to be at high risk for NSF were defined as having stage 4 or 5 chronic renal disease, undergoing dialysis, having acute renal insufficiency (including patients with hepatorenal syndrome), and being in the perioperative liver transplantation period. Patients considered to be at low risk were those who had stage 3 chronic renal disease, children less than 1 year of age, and pregnant patients. NSF was diagnosed by clinical findings and histopathologic evaluation of deep-skin biopsy.

At center A, 35 patients with NSF were identified in the preadoption period; of these, 28 underwent MRI with gadodiamide. The benchmark incidence of NSF at center A was 1/1,750 and the NSF incidence in high-risk patients was 1/33.

At center B, 14 patients with NSF were identified in the preadoption period; of these, 9 underwent MRI with gadodiamide. The benchmark incidence of NSF at center B was 1/1,803 and the NSF incidence in dialysis patients was 1/35.

There were no cases of NSF in the transitional and postadoption periods at either center. ■

MY TAKE

Prevention of NSF Remains a Challenge

It's important to note that the reported decrease in NSF may not have occurred simply because new contrast agents were used. The more restrictive policies on the use of contrast agents might account for the improvement.

Companies that manufacture alternative contrast agents have a clear financial incentive in conducting and reporting such research. This study is by no means definitive, nor should the findings be construed to mean that a flat-out switch to an alternative agent is recommended.

That being said, we've only begun to scratch the surface of NSF. We don't understand the pathophysiology of the disorder, nor do we have any factor other than known renal disease that we can use to stratify patients for NSF risk.

Clearly, we still have a long way to go in addressing the problem of NSF.

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NSF Uncommon After Contrast Agent Black Box Warnings

BY KERRI WACHTER

GAITHERSBURG, MD. — Black box warnings that have been added to the labels of all gadolinium-based MRI contrast agents have reduced the number of reported nephrogenic systemic fibrosis events to almost none during the past year, according to an analysis by Dr. James Kaiser.

"The numbers of new events have tapered dramatically, probably due to public awareness of the association of NSF [nephrogenic systemic fibrosis] with GBCA [gadolinium-based contrast agent] administration," he said at a joint meeting of the Food and Drug Administration's Cardiovascular and Renal Drugs and Drug Safety and Risk Management advisory committees.

Event dates are based on either the date of administration of contrast or the date of diagnosis of NSF.

The FDA began receiving reports of NSF possibly being linked to gadolinium-based contrast agents in 2006, when 194 event dates were reported.

This reporting "probably reflects awareness of the medical community of the potential connection between GBCA administration and NSF and changes in radiologic practice," said Dr. Kaiser of the FDA's office of surveillance and epidemiology. There were 128 reported events in 2007, 55 in 2008, and 6 in 2009 (through September).

In 2007, the FDA asked manufacturers to include a boxed warning on the product labels of all gadolinium-based contrast agents. The warnings caution that patients with severe kidney insufficiency who receive gadolinium-based agents are at increased risk for the development of NSF.

In addition, patients who are in need of a liver transplantation, those who have just undergone liver transplantation, patients who have chronic liver disease, and patients experiencing kidney insufficiency of any severity also have an increased risk of NSF.

Five gadolinium-based contrast agents have been approved for use in the United States: Magnevist (gadopentetate dimeglumine); Omniscan (gadodiamide); OptiMARK (gadoversetamide); MultiHance (gadobenate dimeglumine); and ProHance (gadoteridol).

'The numbers of new events have tapered dramatically,' probably due to awareness of the association of nephrogenic systemic fibrosis with the use of gadolinium-based contrast agents.

As of September 2009, a total of 382 reports of NSF had been associated with Omniscan (GE HealthCare), 195 with Magnevist (Bayer HealthCare), 35 with OptiMARK (Covidien), 1 with MultiHance (Bracco Diagnostics), and 0 with ProHance (Bracco Diagnostics). These numbers are based on reported cases in which a patient had known exposure to only one gadolinium-based contrast agent.

Although there was no formal vote during the committee meeting, the FDA asked the committees to consider whether warning labels should continue to be grouped together as a class or if there was adequate evidence to single out contrast agents that increase the risk of NSF.

"The majority of the group feels that at least two of the agents appear to be different from the other agents," said Dr. Robert A. Harrington, who chairs the Cardiovascular and Renal Drugs Advisory Committee. The majority of the committee members recommended that the use of Omniscan and OptiMARK be contraindicated in patients who have severe kidney dysfunction. However, there was uncertainty as to how to define severe kidney dysfunction.

There was less consensus on whether a third agent, Magnevist, might also warrant contraindication language. As for the other agents, "there was no clear evidence that any one single agent was safe in this patient population," Dr. Harrington noted. ■