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NSF and Omniscan:GE Healthcare Pharmacovigilance Perspective

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Nephrogenic systemic fibrosis (NSF) is a rare, but potentially serious, acquired systemic disease that has been associated with the use of gadolinium-based contrast agents (GBCA) including Omniscan (gadodiamide). It can be a painful and debilitating condition thatmay contribute to a fatal outcome.To date, it has only been reported in patients with renal insufficiency, particularly those with severely impaired renal function with glomerular filtration rate of less than 30 mL/min/1.73m2, who are on or approaching dialysis and those in acute renal failure.At present, there is no evidence that patients without renal impairment are at risk of developing this disease.

The global pharmacovigilance function at GE Healthcare is responsible for reporting of adverse drug reactions, periodic reporting, evaluation of consequences for prescribing information and detection of safety signals.The GE Healthcare safety database includes spontaneous adverse reaction reports, serious reports from clinical trials irrespective of causality, cases published in the literature and reports received from authorities.

At GE Healthcare, all reports concerning nephrogenic systemic fibrosis (NSF), are submitted with no attempt to limit the data by applying an internal set of diagnostic criteria, to help understand this rare disease. Reports are sent worldwide for mandatory regulatory reporting within 15 days after receipt of new information. This article describes activities focused on patient safety and presents data from the global safety database.

NSF Data Collected and Collated by GE Healthcare

In April 2006, when the association between Omniscan and NSF became apparent to GE Healthcare, the global safety database was searched for symptoms and signs compatible with NSF to identify potential cases reported under different terminology. As a result, follow-up information was obtained in two cases.They were subsequently reported as NSF cases.

GE Healthcare has logged and reported all individual case safety reports in which Omniscan was claimed to be associated with NSF.Most of the cases where the age was reported were adult or elderly, specifically two children and two adolescents reported to have developed NSF.

The latency period between last exposure to a gadoliniumbased contrast agent and onset of symptoms was between a few days and several years, most frequently reported was a latency between a few days to a few months.

New Standard Developed to Evaluate Cases

During the period these cases were reported, there was no widely agreed clinical definition of NSF. Therefore reports could not be held to a consistentmedical standard. As a result, GEHealthcare worked with industry partners in conjunction with the American College of Radiology (ACR) to support the development of a common clinical definition of NSF.

However, currently logged cases have not been evaluated against this new standard as much of the patient data collected has been from retrospective analysis of clinical databases. Also many patients are not currently available for clinical follow up. New versions of case reports were created as soon as follow-up information became available. This labour-intensive collection and collation of individual case data from different sources has helped authorities to eliminate duplicate reports from their databases.

However, 157 reports (36%) were not medically confirmed, i.e., provided by lawyers or patients. These reports include basically only the minimum criteria, thus prohibiting duplicate checks. During the past three months, up to the end of July 2008, about 90%of the 70 reports received were not medically confirmed.

The distribution of reported cases among countries is presented in Figure 1. Most of the reports, medically and not medically confirmed, are from the US. The comparatively frequent reports from Denmark are remarkable, even more as they originate from a single institution with the exception of a single case. The reason for this clustering of cases, a common feature, is not yet known.

Our Response to the NSF Alert

As well as GE Healthcare's 'Dear Doctor' letters to health professionals since June 2006, research has advanced both internally and with third party investigators. No cases of NSF with onset have been received since August 2007, indicating the effectiveness of precautionary measures. It is difficult to reliably estimate an incidence rate or to determine the relative safety of GBCA. Factors affecting the number of knownNSF casesmay include different reporting policies between institutions and differences in case definition and handling bymanufacturers.GEHealthcare expedites relevant pharmacovigilance data after receipt of the minimum reporting criteria, thus contributing to rapid signal detection.

Conclusions

It is not yet known what causes NSF and why only a select group of patients, considered to be at high risk, contract the disease. GE Healthcare advises all physicians not to use Omniscan in patients with a glomerular filtration rate <30 mL/min/1.73m2 or in acute renal failure. As there is no clear evidence that any product is safer than another with respect to the risk of NSF in these patients, physicians should use extreme caution whichever product is considered in these patients. The sharp decline in number of cases with recent onset of NSF reinforces the necessity to use gadolinium-based contrast agents including Omniscan in line with the prescribing information.

A full version of this article (including references) is available upon request to editorial@imagingmanagement.org..

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