HealthManagement
Promoting Management and Leadership

Volume 8 - Issue 1, 2008 - Cover Story:Report on Top Papers from MIR 2007 Congress

Chairman During the NSF Cover-Up: When Adverse Event Reporting Becomes a Nightmare

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March 21, 2006, two colleagues from the department of nephrology entered my office. "We have the evidence. The use of gadodiamide impairs our patients" were the heartstopping words. On the Excel spread-sheet before me lay clear evidence that the only common drug given to all the patients who had developed nephrogenic systemic fibrosis (NSF) was gadodiamide. Now, it is said that there are more victims of gadodiamide than after Vioxx before it was withdrawn from the market. Here, I share some of the events that led to a final ban by European authorities on the use of gadodiamide-based contrast-enhanced MRI scans on patients with impaired renal function.

When Adverse Event Reporting Becomes a Nightmare

Since the summer of 2005, there were whispers at our hospital of problems with the contrast agent used in the MR centre. Many patients complained of a bad taste after the injection of gadodiamide. However, our systematic analyses showed that there was no room for doubt: gadodiamide was toxic to certain patients.

The vendor, GE Healthcare, had not informed us about this delayed adverse reaction, despite their official stance that they were active in collecting information about adverse reactions to all their products on an international level. Awaiting a response to a letter I circulated to members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR), and without any external authority providing guidance, we ceased all enhanced MRI exams in patients with reduced renal function. A few days later, Dr. Grobner from Austria informed me that they had also used gadodiamide and in January 2006 published a case report where five out nine patients on haemodialysis developed NSF after exposure to gadolinium. March 30, 2006, the Danish Medicines Agency was informed about our observations.

Where was the Vendor Through all of this?

Studying the literature revealed that from the end of the Eighties gadodiamide was known to have proven stability problems; the ability of the ligand to hold the toxic gadolinium ion was significantly lower than that of most other gadolinium-based contrast agents both in vitro and in vivo. Why had the vendor never told us that? Almost five months later GE finally offered to sponsor a review of the patients concerned, but not an unconditional one. This proposal was clearly ethically questionable. We decided within four weeks to change to another macrocyclic agent in all patients.

Around June 1, 2006, the Health Authorities released a warning about NSF while the vendor released a 'Dear Health Professional' letter in the US, though not in Europe, a cautious statement that there 'might' be a problem. This issue is under scrutiny presently, at a Jacksonville, Florida court where GE is now accused of negligence. At congresses, GE continued to announce that gadodiamide was a safe drug despite the 'Dear Health Professional' letter. How could I go further with my investigation to ensure patient safety?

Reports Flood in About Adverse Reactions

Mid-August I sent an email to all the members of ESUR asking whether they had heard about NSF. The advantage of ESUR is that it has members all over the world. The response was worrying. Within two weeks I had received reports about 150 cases of NSF after exposure to gadolinium contrast agents. I contacted the respondents and asked which contrast agent they used, independent of whether they had said "no

cases" or "yes, we had cases". In 95% of the cases, gadodiamide was the agent used.

I contacted the Editor-in-chief of European Radiology, Prof. Albert Baert. He agreed that it was an important message that needed to be published as soon as possible and within six weeks my editorial was available on the internet – the first warning in a radiological journal. Meanwhile, our analysis confirmed our initial conclusion that macrocyclic agents were preferable with regards to stability. We found it unethical to continue gadodiamide in all patients.

Reinstating a Safer MRI Exam

We could not continue diminishing access to enhanced MRI exams for end-stage renal failure patients. After a medical technology assessment where we evaluated the alternatives, we commenced again with MRI. Factors that were included in the assessment were:

• Diagnostic quality (worse, equal or better to enhanced MRI);

• Procedural complications;

• Morbidity and mortality of haemodialyses in untrained patients;

• Acute non-renal adverse reactions;

• Acute renal adverse reactions, and

• Delayed reactions.

In most instances we concluded the risk from an alternative exam outweighed the risk of NSF after exposure to a macrocyclic agent in MRI doses. We still discuss whether it was beneficial to do peripheral arteriography as a pretransplant exam despite having shown that we found silent vascular stenosis in about 5% of these patients.

In Denmark, Omniscan was approved for general MRI of the whole body in doses up to 0.3 mmol/kg, also in patients with CKD 5 (< 15 ml/min) including dialysis. There was no warning in the SPC until February 7, 2007, when the EMEA decided that it was contraindicated to use Omniscan in patients with a GFR below 30 ml/min. The local situation had been settled within three to four months. Since we reintroduced this type of MRI exam, we have not seen a single case of NSF.

International Colleagues Weigh In

Increasing numbers of international colleagues confirmed that they had seen nephrogenic systemic fibrosis in patients with end-stage renal failure after exposure to gadolinium-based contrast agents, in particularly gadodiamide. With time, we also found more cases (August 1, 2007: 27 further cases after gadodiamide). Cases with other products were also reported. As of August 1, 2007, a total of 123 cases of NSF where authors have looked at the gadolinium exposure have been documented. 118 of these cases had gadodiamide as a triggering agent. It substantiates our findings. After we reintroduced enhanced MRI with a macrocyclic agent we have not seen a single case of NSF.

Why the Smokescreen?

The burden of investigating this event was left to concerned Chairpersons such as myself. The consequence of taking such a stand against worldwide entities, however, was the negative feedback I experienced. I get invitations to lecture at many institutions. A common response was how late radiologists became aware of the problem. They felt someone tried to diminish the problem.

Recommendations are Recognised

During this time, the European authorities instituted a ban on the use of gadodiamide in patients with reduced renal function; exactly what I had recommended in a paper that was labeled as 'misleading to health professionals' by industry executives. Also at this time, rumours came out that specialists had warned the company about bringing gadodiamide to market. It was not for human use. Surprisingly, this was confirmed at the NSF session at the international congress of MRI in Berlin. In February 2007, the European Authorities contraindicated the use of gadodiamide in patients with reduced renal function. At last, we had official recognition of our observations.

Conclusion

We hear much about 'corporate ethics' in press releases and through the media. But a commercial company will always look at their balance sheet in these considerations, which leads me to quote George Orwell, as follows: "**In a time of universal deceit, telling the truth is a revolutionary act**".

Published on : Sat, 1 Mar 2008