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History of Nephrology

Gadolinium-induced nephrogenic systemic fibrosis: the rise and fall of an iatrogenic disease

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Abstract

Background. In 2006, nephrologists in Denmark unexpectedly identified chronic kidney disease (CKD) patients with a new syndrome, nephrogenic systemic fibrosis (NSF). Subsequently, 1603 NSF patients were reported to the Food and Drug Administration. Sixty hospitals in the USA account for 93% of these cases, and two hospitals in Denmark account for 4% of these reports. We review Denmark's identification and subsequent rapid eradication of NSF.

Methods. NSF reports from clinicians, the Danish Medicines Agency (DMA) and gadolinium-based contrast agents (GBCAs) manufacturers were reviewed (2002–11).

Results. In 1994, the DMA approved a non-ionic linear GBCA, gadodiamide (0.1 mmol/kg), for magnetic resonance imagings (MRIs), with a renal insufficiency contraindication. In 1996, 0.3 mmol/kg dosing received DMA approval. In 1998, the DMA removed renal contraindications. In 1997 and 2002, radiologists at Skejby Hospital and Herlev Hospital, respectively, began performing gadodiamide-enhanced magnetic resonance angiography scans (0.3 mmol/kg) of CKD patients. In 2005, Herlev clinicians requested assistance in evaluating etiological causes of NSF occurring among 10 CKD patients who had developed NSF. This investigation, focusing on infectious agents, was inconclusive. In 2006, Herlev clinicians reported that of 108 CKD patients who had received gadodiamide-enhanced MRI, 20 had developed probable NSF. Herlev radiologists voluntarily discontinued administering gadodiamide to all patients and no new NSF cases at Herlev Hospital developed subsequently. After meeting with Herlev radiologists, Skejby radiologists also discontinued administering gadodiamide to all patients. In 2007, the European Medicines Agency and the DMA contraindicated gadodiamide administration to CKD patients. In 2008, in response to these advisories, radiologists at the other 36 Danish hospitals discontinued administering gadodiamide to all patients, following on practices adopted at Skejby and Herlev Hospitals. In 2009, clinicians at Skejby Hospital reported that a look-back survey identified 33 CKD patients with NSF developing after undergoing GBCA-enhanced MRIs between 1999 and 2007. In 2010, an independent review, commissioned by the Minister of Health, concluded that the DMA had erred in rescinding gadodiamide's renal insufficiency contraindication in 1998 and that this error was a key factor in the development of NSF in Denmark. In 2011, three NSF cases associated with macrocyclic GBCA-associated NSF and three NSF patients with Stages 3 and 4 CKD disease from Skejby Hospital were reported.

Conclusion. A confluence of factors led to the development and eradication of NSF in Denmark.

Keywords: chronic kidney disease; gadodiamide; gadolinium; magnetic resonance angiography; nephrogenic systemic fibrosis

Introduction

Nephrogenic systemic fibrosis (NSF) is a new and rare syndrome characterized by fibrotic skin, muscle contractures, decreased range of joint motion and organ fibrosis [1, 2]. Between 1997 and 2000, this syndrome was first diagnosed in 14 chronic kidney disease (CKD) patients who were receiving hemodialysis in California [2]. It can be painful, debilitating and even fatal [1].

In January 2006, an Austrian nephrologist reported that of nine CKD patients who had triple-dosed gadolinium-based contrast agent (GBCA)-enhanced magnetic resonance imaging (MRI) five developed NSF [3]. In March, a nephrologist at Denmark's Herlev Hospital reported 20 CKD patients developing NSF following GBCA-enhanced MRIs

Table 1. Gadolinium-containing agents and commercial names

Generic name	Brand name	Acronym	Chemical structure	Charge	Risk for NSF[a]
Gadodiamide	Omniscan	Gd-DTPA-BMA	Linear	Non-ionic	High
Gadoversetamide	OptiMARK	Gd-DTPA-BMEA	Linear	Non-ionic	High
Gadopentetate dimeglumine	Magnevist	Gd-DTPA	Linear	Ionic	High
Gadobenate dimeglumine	MultiHance	Gd-BOPTA	Linear	Ionic	Medium
Gadoxetic acid disodium salt	Eovist, Primovist	Gd-EOB-DTPA	Linear	Ionic	Medium
Gadofosveset trisodium	Vasovist, Ablavar	Gd-DTPA	Linear	Ionic	Medium
Gadoteridol	ProHance	Gd-HP-DO3A	Cyclic	Non-ionic	Low
Gadobutrol	Gadovist, Gadavist	Gd-BT-DO3A	Cyclic	Non-ionic	Low
Gadoterate meglumine	Dotarem[b]	Gd-DOTA	Cyclic	Ionic	Low

[a]Risk as noted by the EMA's Scientific Advice Group.
[b]Not approved by the FDA

[4]. All had received gadodiamide, a non-ionic linear chelated GBCA. Gadodiamide has been the second most commonly administered GBCA, with 40 million units of gadodiamide having been administered in 90 countries since 1993 [5] (Table 1). Also, in March, Herlev Hospital radiologists voluntarily and immediately substituted a cyclic GBCA for gadodiamide. In 2007, European regulators concluded that administering gadodiamide to all patients was contraindicated [5]. The Food and Drug Administration (FDA) has received 1630 NSF reports, 4% from Skejby and Herlev Hospitals in Denmark and 93% from 60 hospitals in the USA [5, 7]. Herein, we review the Danish NSF outbreak. We also discuss the international benefits resulting from rapid dissemination of information on the Danish cases [3–34].

Materials and methods

Information was obtained from gadodiamide's manufacturers, Denmark's Patient Insurance Agency and the FDA (2002–10); Danish Medicines Agency (DMA) reports (2006 and 2008); Danish publications (2006–11); notifications from DMA, FDA and European Medicines Agency (EMA) (2006–10) and an independent report commissioned by Denmark's Health Minister (2010) [3–34]. The case definition included clinically suspected or biopsy-confirmed NSF [1]. The project received Institutional Review Board approval from Northwestern University.

Results

Regulatory history

In 1994, gadodiamide was approved by the DMA at a dose of 0.1 mmol/kg, with a contraindication initially for 'reduced renal function' [4, 5] and subsequently for 'severe renal insufficiency'. The contraindication was based on the absence of safety data among patients with reduced renal function [4, 5]. In 1995, the DMA approved 0.3 mmol/kg dosing for evaluating brain metastases [4, 5]. In 1996, the DMA extended 0.3 mmol/kg dosing to general MRIs [4, 5]. In 1998, the renal insufficiency contraindication was revoked, based on a Herlev report identifying few side effects among 49 Norwegian and Danish CKD patients receiving gadodiamide (0.1 mmol/kg dosing)-enhanced MRI scans [4, 5, 8]. The manufacturer did not provide safety data for gadodiamide beyond 0.1 mmol/kg dosing.

Skejby Hospital actions (1997)

Skejby Hospital radiologists endorsed administration of GBCA to CKD patients, based on insights that the technique outperformed MRIs without contrast enhancement with respect to scan time and visualization performance [9]. Subsequently, 565 patients with reduced renal function had undergone GBCA-enhanced MRIs at Skejby Hospital.

Initial cases (2002–05)

In 2002, a nephrologist reported to the DMA and gadodiamide's manufacturer a 48-year-old CKD male patient with severe muscle pain and oliguria beginning the day after undergoing a gadodiamide-enhanced magnetic resonance (MR) angiography (MRA) scans at Herlev. Shortly thereafter, two clinicians independently reported a 55-year-old CKD female patient experiencing severe skin, joint and muscle pain beginning immediately after undergoing a gadodiamide-enhanced MRA at Herlev. Both patients experienced oliguria following the procedure, requiring conversion from peritoneal dialysis to hemodialysis. Within weeks, the second patient was unable to walk due to extreme muscle and joint stiffness. In 2003, this patient died from a pulmonary embolism. The Patient Insurance Agency ruled that death resulted from gadodiamide toxicity and awarded a financial settlement. (Subsequently, biopsy materials confirmed NSF diagnosis [10].)

In 2003, a Herlev resident physician reviewed radiology and nephrology records for 104 CKD patients following gadodiamide-enhanced MRAs (0.3 mmol/kg) [11]. While two patients converted from peritoneal dialysis to hemodialysis (subsequently diagnosed as NSF), no other serious adverse events occurring within 2 weeks of gadodiamide administration were noted. This study concluded that gadodiamide-enhanced MRA was useful for evaluating arteries in patients with peripheral vascular disease [11]. Herlev nephrologists continued endorsing gadodiamide-enhanced MR examinations (0.3 mmol/kg), standard dosing for peripheral runoffs with available scanners.

In 2005, a Herlev resident physician, concerned that unknown exposures caused 10 CKD patients to develop NSF, requested assistance from the Board of Health epidemiologists [12]. Five patients had skin biopsies consistent with NSF. The investigation, focusing on infectious causes, was inconclusive.

Gadodiamide–NSF association (2006)

In January, an Austrian report described five patients developing NSF shortly after undergoing GBCA-enhanced MRIs [3].

Table 2. Opportunities to recognize the association of gadodiamide administration with NSF development in Denmark (2002–06) [6]

Event	Action	Initial response	Later action
2002			
Index case develops acute skin toxicity immediately after undergoing a gadodiamide-enhanced MR at Herlev Hospital	Case reported to Danish Medicines Agency	Patient's findings are categorized by the manufacturer as being consistent with underlying disease	Manufacturers are no longer asked to adjudicate adverse event report descriptions
Second NSF case undergoes skin biopsy	Pathologist reviews the biopsy	Pathologist reads the biopsy as being consistent with foreign body reaction	Re-read of the biopsy in 2006 confirms the diagnosis of NSF
Second NSF case	Case reported to the manufacturer of gadodiamide by a dermatologist and a rheumatologist	Manufacturer classifies the case as exacerbation of underlying autoimmune disease	Biopsy reviewed by Shawn Cowper of Yale University Medical School and confirms NSF diagnosis
2003			
Second Danish NSF case dies and Danish Patient Insurance Association awards large financial compensation	Danish Patient Insurance Association sends report of financial compensation to the manufacturer and states that patient's death was probably a result of the gadodiamide administration	Manufacturer classifies the death as a consequence of underlying immunological disease	Patient diagnosed with NSF after death—in 2006
Manufacturer updates Periodic Safety Update Report (PSUR)	The PSUR does not list the first two NSF patients' deaths as serious adverse drug reactions	The PSUR listing could have included the 2002 and 2003 cases as potential fatal adverse drug reactions	Patient's deaths re-classified as a serious adverse drug reaction in 2006
2004			
Similar clinical findings for a CKD patient undergoing a gadodiamide-enhanced MR procedure in Texas	Radiologist in Texas telephones manufacturer to query whether any similar cases have been reported	Manufacturer does not link this case with the two index cases from Herlev Hospital in 2002	FDA requests in 2006 that the manufacturer review this case for possibility of NSF diagnosis
Manufacturer sends a PSUR to Danish regulatory authorities	All serious adverse drug reactions identified by the manufacturer are described	Details of the two Danish patients and the one Texas patient are not included in this 2004 PSUR prior to 2006	The three patients are re-classified in 2006 as having had biopsy confirmed NSF and are added to a 2006 PSUR
2005			
A radiology resident published a Herlev Hospital retrospective study of 104 CKD patients who underwent gadodiamide-enhanced MR procedures in 2002 and 2003	Medical records and angiograms are reviewed by radiologists at Herlev Hospital	Records of only two patients identify skin and muscle changes following the MR procedure. The records were reviewed for evidence of nephrotoxicity and changes in vascular findings within days of the procedure. Nephrologists attribute the changes to exogenous iron administration	After examining most of these patients in late 2006, the diagnosis of NSF is biopsy confirmed in eight patients who had gadodiamide administered between 2003 and 2005
A nephrology resident suspects that gadolinium might be the cause of acute skin changes and neuropathic symptoms of peritoneal dialysis patient exposed to gadodiamide in autumn 2005	Skin biopsy sent to a pathologist for examination for gadolinium in 2005	Methodology to identify gadolinium in skin biopsy is unavailable in 2005	Scanning electron microscopy identifies gadolinium in biopsy in 2007
Nephrologist suspects that common exposure might account for skin, muscle and joint changes in 10 CKD patients at Herlev Hospital	Medical record review is done. Summary table created in 2005 includes clinical findings and potential exposures	Gadolinium is listed as an exposure on only 2 of the 10 case summaries in the 2005 summary table	2006 re-review of the medical records identifies gadodiamide exposure on all 10 patients
A fourth CKD patient develops acute toxicity following the gadodiamide-enhanced MR procedure	Clinicians in Germany report the details of this patient to the gadodiamide manufacturer of acute toxicity following the gadodiamide-enhanced MR procedure	Clinical details are not linked by safety personnel at the manufacturer with the prior three reports	2006 re-review classifies this patient as having had NSF
2006			
A Herlev Hospital nephrologist identifies 20 CKD patients with clinical diagnoses of NSF—all had undergone a gadodiamide-enhanced MR imaging procedure (early March 2006)	The Hospital nephrologist, Peter Marckmann, telephones the Danish Medicines Agency and describes the 20 CKD patients as having clinical diagnoses of NSF—all had undergone a gadodiamide-enhanced MR imaging procedure (early March 2006). These reports form the basis for the Danish Medicines Agency dissemination of a statement of concern and are forwarded to the European Medicines Agency, FDA, and to gadodiamide's manufacturer	All 20 patients were later described in a written communication by the nephrologists to the DMA as clinically suspected NSF cases (Late March 2006). These reports form the basis for the Danish Medicines Agency dissemination of a statement of concern and are forwarded to the European Medicines Agency, FDA, and to gadodiamide's manufacturer. (May 2006)	Skin biopsies confirm the NSF diagnosis in 13 of these patients. Findings are published as a rapid communication in August in the *Journal of the American Society of Nephrology* [22] in 2006.

Continued

Table 2. *Continued*

Event	Action	Initial response	Later action
Radiologists at Skejby Hospital hold a conference on NSF in 2006 (hosted by the manufacturer of gadodiamide)	No cases of NSF at Skejby Hospital based on clinician recall were identified. Radiologists conclude that gadolinium is unlikely to be the cause of NSF	Radiologists continued to administer gadodiamide to CKD Stages 4–5 patients until October 2006	2009 medical record re-review augmented by patient examination identifies 33 possible gadodiamide-associated NSF patients (10 are subsequently biopsy confirmed)

The specific GBCA was erroneously identified as gadopentetate dimeglumine. (This error was corrected in print in June 2006.)

In March, a Herlev Hospital nephrologist, Peter Marckmann, reported to the DMA that gadodiamide was a likely cause of NSF, based on his identification of 20 CKD patients developing NSF following gadodiamide-enhanced MRAs [4, 5, 10, 13]. Herlev radiologists voluntarily and immediately discontinued gadodiamide-enhanced MR investigations to all patients, substituting cyclic GBCAs [6, 12, 13].

In June 2006, NSF was discussed for the first time in the European Union's Side Effects Committee. At the time, the European Union had knowledge of the 20 Danish cases, 5 cases in Austria and an FDA database with 200 possible NSF cases from worldwide sources. The Committee acknowledged that there was no consensus on diagnostic criteria; documentation was incomplete in many cases particularly about which GBCA and what dose had been administered and whether a patient possibly could have received several different gadolinium-containing contrast agents. The Committee also considered the number of side effect reports to be very low compared to the information on the total use of gadodiamide and NSF reports were primarily from two European Union nephrology departments, despite wide use of gadodiamide internationally. Hence, there was skepticism with regard to a correlation between gadolinium and NSF.

In August, clinicians at Skejby Hospital reported that they had not diagnosed a single NSF case, despite routinely imaging CKD patients who were transplant candidates. Also, gadodiamide's manufacturer advised 300 Danish radiologists and 114 Danish nephrologists in a letter that an NSF–gadodiamide association was observed among CKD patients at Herlev Hospital and that no causal relationship had been identified [12].

On 20 September, DMA met with gadodiamide's manufacturer concerning NSF reports received from Herlev Hospital [4, 5, 12]. The DMA announced initiating an investigation and a causal relationship between gadodiamide and NSF was uncertain [4, 5, 12]. At the Danish council meeting on 27 September, a DMA representative said that it was problematic that Herlev Hospital radiologists had advised radiologists to avoid gadodiamide for CKD patients as a causal relationship had not been confirmed [12].

On 24 October, a conference on the NSF situation in western Denmark was held at the MRI center at Skejby Hospital. In attendance were Marckmann, representatives of the manufacturers of gadodiamide and gadopentetate dimeglumine and nephrologists from Skejby Hospital [4, 5, 12]. Nephrologists from Skejby Hospital reported that unique conditions at Herlev Hospital might have resulted in NSF cases at that hospital since cases were not recognized at other Danish hospitals. Nonetheless, for precautionary reasons and based on the Herlev Hospital information, Skejby Hospital discontinued administering gadodiamide [4, 5, 12, 14].

2007 European responses

In January, the Pharmacovigilance Working Party of EMA's Committee for Medicinal Products for Humans (CMHP) recommended contraindicating gadodiamide among severe renal disease patients [5].

In February, the European Adverse Drug Reaction Council issued a strict contraindication against administering gadodiamide to severe renal disease patients and advised caution with other GBCAs [5]. The DMA issued new recommendations reflecting the Council's decision.

In May, Herlev Hospital clinicians reported that among Stage 5 CKD patients, lifetime gadodiamide doses were 0.44 mmol/kg in 19 NSF cases versus 0.34 mmol/kg in 19 controls. Patients with severe versus less severe NSF received greater doses (0.57 versus 0.33 mmol/kg). NSF patients had a mean 14-day symptom-free period [15].

In June, the Council contraindicated administering another linear-chelated GBCA, gadopentetate dimeglumine, to severe CKD patients [5]. In July, the EMA's CMHP approved gadovertisamide with the same renal contraindications [5].

In October, the European Society of Urogenital Radiology disseminated guidelines identifying three linear-chelated GBCAs as high NSF risk [16, 17].

In December, the Scientific Advisory Group for Diagnostics of EMA's CMHP adopted this categorization [12].

DMA reviews regulatory decisions (2008)

In February, the EMA endorsed its Scientific Advisory Group classification of GBCAs into three NSF risk groups and among high-risk GBCAs, NSF risks were highest with gadoversetamide and gadodiamide [4, 12]. In response to the EMA and DMA regulatory advisories contraindicating administration of linear-chelated GBCAs to CKD patients, Danish radiologists at 36 Danish hospitals adopted the practices that had been voluntarily implemented in 2006 at the two remaining Danish hospitals (Skejby and Herlev Hospitals) and discontinued administering non-ionic linear-chelated GBCAs to all patients, including CKD patients.

Also, in February, Denmark's Secretary of Health commissioned DMA review gadodiamide's regulatory handling [4, 12]. The report, submitted in March, concluded that the DMA had acted responsibly in approving gadodiamide in 1994 with a contraindication for severe renal insufficiency patients and in revoking this contraindication in 1998. The DMA indicated that upon reviewing Periodic Safety Update Reports, concerns regarding gadodiamide–NSF associations surfaced in 2006 [4, 12]. The DMA requested gadodiamide's manufacturer comment on allegations that safety-related information had been withheld from

Herlev radiologists. The manufacturer stated that *in vitro* and *in vivo* assessments did not support safety concerns and they had not 'held back' stability information [4, 12].

In March, Herlev Hospital clinicians reported higher NSF rates with gadodiamide versus other GBCAs (3–7 versus 0–1% per injection) [17] and severe NSF risk factors of higher cumulative gadodiamide doses, higher erythropoietin dosage and being on hemodialysis [18]. They reported an 18% NSF rate among 88 Stage 5 CKD patients versus 0% among 102 Stages 1–4 CKD patients [19].

In April, the Health Minister requested regional medical councils contact NSF patients [4, 12]. Also, gadodiamide's manufacturer initiated a libel lawsuit in London against a Herlev Hospital radiologist who presented NSF findings at Oxford [20].

Skejby NSF cases (2009)

In January, clinicians from Skejby Hospital reported that in-person patient examinations and medical record reviews had identified 10 Stage 5 CKD patients with biopsy-confirmed NSF and 24 with clinically suspected NSF [12]. All had undergone GBCA-enhanced MRAs between 1999 and 2006 and most had received gadodiamide. (No NSF diagnoses had been listed in the patient's medical records, hence the in-person examination was an important factor in identifying these patients.)

In February, Danish Parliament's Health Committee summoned the Health Minister, requesting background about the 1998 DMA decision to rescind the contraindication against gadodiamide for severe renal insufficiency patients and about two NSF cases reported in 2002 to the DMA. The Minister commissioned an independent investigation of gadodiamide decisions by DMA, the Board of Health and the Health Ministry, which began in October 2009.

In September, Danish nephrologists described occasional NSF remission after recovery from acute renal failure or following kidney transplantation [22].

The independent investigator's report (2010)

In February, the libel lawsuit filed by gadodiamide's manufacturer against a Herlev radiologist was settled [12, 20].

In April, the DMA reported a national survey which identified 67 living NSF cases—36 following gadodiamide, 26 following gadodiamide and another GBCA and 5 following GBCAs other than gadodiamide. The national survey did not include patients undergoing radiography with GBCA. Also, the records of the patients were surveyed, while the skin in every patient was not inspected. The Patient Insurance Agency paid claims to 41 living disabled NSF patients (36 from gadodiamide, 4 from gadopentate dimeglumine and 1 from gadofosveset trisodium). The Agency received 86 claims—28 were rejected and 17 are under study. Rejection does not necessarily mean NSF was absent—some rejections were because GBCA exposure did not result in disability [12].

In November, the Health Secretary informed Denmark's Parliament that gadodiamide's manufacturer had violated Danish law by not reporting to the DMA the death of the 55-year-old CKD patient who developed skin, joint and muscle abnormalities after undergoing a gadodiamide-enhanced MR in 2002 [23]. As noted earlier, the case that had been reported by two physicians (independently) to DMA in 2002. The report from the independent attorney's review of Danish regulatory decision found serious errors by the Board of Health and DMA accompanying the 1998 removal of CKD as a contraindication against gadodiamide, that DMA committed errors by withholding information from the Health Ministry in reply to Parliament's 2009 queries about the DMA's removal of the contraindication and that the DMA committed errors during review of toxicity reports submitted between March and August 2006 [12]. The EMA's CMHP indicated that among high-risk linear-chelated GBCAs, additional NSF risk factors included dose, frequency and duration of use [24].

Autopsy findings (2011)

In March, an autopsy report from Danish and US collaborators identified gadolinium phosphate deposits in cerebellum, skin, kidney, skeletal muscle and lymph nodes of NSF patients but not among patients unexposed to GBCAs and rarely among GBCA-associated CKD patients without clinical NSF signs [25].

In July, the manufacturer of gadodiamide provided DMA a copy of an internal draft report from 1994 identifying dissociation of gadodiamide in serum. (available at http://www.ugeskriftet.dk/portal/page/portal/LAEGERDK/UGESKRIFT_FOR_LAEGER?public_visningsType=5&public_modtager=0&public_forrigeVisningsType=4&public_nyhedsId=65909&public_afsender_gruppe=9,13).

In August, the journal *Academic Radiology* published a research letter from a Danish nephrologist and a radiologist who revisited a 1998 study which had concluded that gadodiamide could be administered safely to CKD Stage 5 patients [8, 35]. Safety assessments such as skin inspection after the follow-up were not done and only a single gadodiamide 0.1 mmol/kg dose was administered. With present knowledge, they report that the 1998 conclusion is not justified and gadodiamide is unsafe in CKD.

In October, a case–control study from clinicians at Skejby Hospital reported on 565 renal insufficiency patients with GBCA exposure between 1997 and 2009 [21]. They identified 17 NSF cases and 17 controls without signs of NSF. NSF prevalence was 4.7%, highest among CKD Stage 5 patients exposed to GBCA and undergoing hemodialysis or peritoneal dialysis. Three NSF cases were identified among patients with CKD Stages 3 and 4. Three patients developed possible NSF after macrocyclic GBCA exposure, although pathological findings for these patients do not fulfill current criteria for NSF [36]. NSF cases had a tendency to have higher serum phosphate concentrations than GBCA-exposed controls. They concluded that their updated findings indicated that CKD Stages 3 and 4 patients were at risk for NSF and that NSF may be triggered by macrocyclic GBCAs, although uncertainty over pathological confirmation of the NSF diagnoses limits the generalizability of their findings.

Discussion

At Skejby and Herlev Hospitals, the first gadodiamide-associated NSF cases occurred in 1998 and 2002, respectively, reached a maximum in 2005 and declined to one by 2008 [4, 12]. Throughout Denmark, no new NSF case has been reported since December 2008. (In the USA, home to 93% of reported NSF cases, the first case occurred in 1997, maximum reports of new cases were reached in 2006 and no new NSF cases were reported after 2009 [28, 30].) Patient, physician, hospital, product, regulatory and country considerations account for the emergence and disappearance of NSF in Denmark (Table 2).

As noted by the EMA in 2007 and FDA in 2010, GBCA-associated NSF rates were highest with linear-chelated GBCAs [24]. Scanning electron microscopy identified gadolinium in biopsies from NSF patients at Herlev [31]. Inductively coupled mass spectrometry confirmed the gadolinium [35]. Metal ions compete with gadolinium for ligand binding, a phenomenon called transmetallation. Impaired renal function and increased temperatures enhance transmetallation, by increasing linear-chelated GBCA's half-life [8, 37]. Rodent and human studies demonstrate higher residual gadolinium levels with linear versus cyclic gadolinium chelates. Gadodiamide is associated with 93% of Danish and 70% of US NSF cases, while the linear GBCA gadopentate dimglumine is associated with 5% of Danish and 20% of US cases [4, 28, 30].

In Denmark in 1996, the DMA granted approval for gadodiamide at 0.3 mmol/kg dosing for general usage, while maintaining a contraindication against administration to CKD patients. In 1998, the DMA revoked this contraindication. Subsequently, Skejby Hospital and Rigshospital radiologists endorsed GBCA administration (dosages as high as 0.5 mmol/kg) for MRAs. Skejby and Rigshospital radiologists and vascular surgeons reported in 2001 that 'there is no [GBCA] nephrotoxicity and maximum doses can be used safely in patients with renal insufficiency' [9]. In 2001, Herlev purchased an MR scanner. In 2002, Herlev clinicians endorsed gadodiamide (0.3 mmol/kg) for CKD patients attempting to improve transplant recipient selection. While gadodiamide was administered at 38 hospitals in Denmark, most NSF reports were from Skejby and Herlev Hospitals, where gadodiamide 0.3 mmol/kg dosing to CKD patients was administered during NSF outbreak years [4, 5, 7, 10, 35]. Five Danish hospitals have renal transplantation programs (including Skejby and Herlev Hospitals), most CKD patients in Denmark are seen at these five hospitals and high doses of gadodiamide were administered predominantly at Skejby and Herlev Hospitals. Also, Danish NSF investigation evaluated patients for NSF who were alive in 2009 and 2010. Several NSF patients may have died between 1998 and 2009 without being diagnosed with NSF and thus the actual number of NSF patients at the 38 Danish hospitals may have been greater than reported.

Our findings help explain the development and eradication of NSF cases in the USA and few cases in other countries. The manufacturer of gadodiamide reported to the FDA that NSF cases had been identified at 60 United States' hospitals (all of which had large CKD and renal transplantation programs), although gadodiamide had been administered at 2100 United States' hospitals [7, 27–30]. Gadodiamide-associated NSF in the USA is an example of toxicities associated with 'indication creep'—drug use in 'off-label' indications [38]. After gadodiamide received FDA approval for 0.3 mmol/kg dosing for central nervous system MR imaging and for 0.1 mmol/kg dosing for MR body imaging in 1996, physicians endorsed 0.3 mmol/kg dosing 'off-label' for MRAs outside the central nervous system or during radiographic studies. Concurrently, multistationary MRAs requiring multiple bolus injections or one large bolus of GBCAs were being developed [39]. Gadodiamide safety would have been improved if practice had been guided by regulatory FDA approvals [40]. No NSF occurrences at most United States' hospitals may be due to infrequent 'off-label' administration of linear-chelated GBCAs at 0.3 mmol/kg dosing to CKD patients.

NSF occurs among patients with acute kidney injury, with CKD Stages 4 and 5 or among hemodialysis patients, particularly those with concomitant liver disease [1]. This observation provides rationale for evaluating renal function prior to administering high-risk GBCAs [41].

Our findings explain no new NSF cases being reported since 2007 in Denmark and 2009 in the USA. In Denmark, the peak number of NSF cases was in 2005, decreasing to zero by 2008, following decisions to substitute more stable GBCAs for gadodiamide among CKD patients. In the USA, FDA in September 2010 issued a requirement that patients be screened for CKD prior to undergoing GBCA-enhanced MR scans and issued a contraindication against administering linear-chelated GBCAs to CKD patients [27]. Peak United States NSF reports occurred in 2006. Following the FDA's 2006 NSF notification of the Danish outbreak, GBCA administration to CKD patients decreased and, subsequently, NSF identification decreased precipitously. No new United States NSF cases were identified after 2009, when clinicians voluntarily discontinued administering linear-chelated GBCAs to CKD patients [28].

Our study has limitations. GBCA doses administered at hospitals other than Skejby and Herlev Hospital were not available for review. Additional NSF cases may have occurred and may not have been diagnosed or reported to regulatory agencies. The 2010 national survey in Denmark found 67 patients, but the 2009 Skejby NSF notification included at least 15 deceased patients with signs and symptoms of NSF according to their medical records. An unknown number of deceased patients may have had NSF without any notations of clinical findings in their medical records. Therefore, the actual number of NSF patients in Denmark, a country of 5.5 million individuals, may be larger than the 82 patients reported to date to the DMA [12]. Finally, information included in the 2010 Attorney Report on NSF has not been available previously, and hence, a comprehensive analysis of NSF in Denmark was not possible previously.

Despite these limitations, our review of the Danish NSF outbreak provides insights into the emergence of NSF as a clinical entity in Denmark in 1998 and its disappearance 10 years later. These insights also apply to the NSF experience in the USA during the years 1997 when NSF cases first developed through 2009 when the last NSF case in the USA occurred as well as to the observation that few NSF cases have been reported from countries other than Denmark and the USA. Clinicians should be cognizant of GBCAs' risks and benefits. NSF fears should not lead to denial of enhanced MR imaging examinations with lower risk stable GBCAs, when clinically appropriate [34].

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