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Original contribution

Influence of excess ligand on Nephrogenic Systemic Fibrosis associated with nonionic, linear gadolinium-based contrast agents

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ABSTRACT

Background: The molecular structure, charge, thermodynamic and kinetic stability are approximately the same for gadodiamide and gadoversetamide, the main substantive difference is that gadodiamide is manufactured with 5% free ligand to form Omniscan® and gadoversetamide with 10% free ligand to form OptiMARK®.
Purpose: To determine the relative risk of Nephrogenic Systemic Fibrosis (NSF) between gadodiamide (Omniscan®) and gadoversetamide (OptiMARK®) and to explore the potential contribution of the amount of excess ligand added to their commercial formulations.
Materials and methods: In this retrospective observational study, the number of doses and NSF cases associated with these agents were calculated based on two different approaches: the number of doses was determined based on pharmaceutical companies' information, and the number of unconfounded NSF cases was obtained from the previously published literature based on a legal database. A second analysis estimates the number of doses and NSF cases from the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).
Results: Approximately 87 million and 12 million doses of Omniscan® and OptiMARK®, respectively, have been administered worldwide since their original approval for use in the various countries throughout the world. A total of 197 and 8 unconfounded cases of NSF have been reported with Omniscan® and OptiMARK®, rendering an incidence of 2.3/million and 0.7/million for these agents, respectively. The FAERS analysis suggested reported incidences of 13.1/million and 5.0/million.
Conclusion: There is an approximately 3-fold greater incidence of NSF from Omniscan® than OptiMARK®. The difference in incidence might reflect the lesser quantity of added free ligand to the formulation of Omniscan®.

1. Introduction

Nephrogenic Systemic Fibrosis (NSF) is a multisystemic debilitating disease that appears to occur exclusively in patients with renal impairment. There is a well-established association between NSF and exposure to gadolinium-based contrast agents (GBCA) [1–4]. Most cases of NSF reported in the literature were associated with the administration of linear agents, in particular, the nonionic linear gadodiamide (Omniscan®; GE Healthcare) and gadoversetamide (OptiMARK®; Guerbet), and the ionic linear agent, gadopentetate dimeglumine (Magnevist®; Bayer HealthCare Pharmaceuticals) [5–11]. Since mid-2009, after restrictive guidelines regarding GBCA administration were instituted, no new cases of NSF with linear agents were reported [1–4,12,13]. NSF cases are usually considered as unconfounded if the individual was exposed to only one GBCA prior to NSF diagnosis, and as confounded, if there was documentation of exposure to two or more GBCAs.

Omniscan® and OptiMARK® are both linear open-chain non-ionic agents that have comparable thermodynamic and kinetic stability (Log K_{therm} of 16.9 and 16.6; Log K_{cond} of 14.9 and 15.0, respectively) [14] but differ in the amount of excess free chelator/ligand. Omniscan contains approximately 12 mg/mL of excess ligand (~5%), whereas OptiMARK is formulated with 28.4 mg/mL (~10%) [5–11,14].

The kinetic stabilities of GBCAs in human serum can be represented by their dissociation rate constants. Wedeking et al. have provided a thorough explanation of the relation between the thermodynamic stability, the conditional stability, the kinetic stability and the retention of gadolinium (Gd) for the various GBCAs [1–4,15]. Without excess

Abbreviations: AE, adverse event; AER, Rate of adverse events per dose in clinical trials; CI, 95% confidence interval; GBCA, gadolinium-based contrast agents; FAERS, Food and Drug Administration Adverse Event Reporting System; FDA, Food and Drug Administration; NSF, Nephrogenic Systemic Fibrosis; RR, relative risk

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ligand, Gd-DTPA-BMA (gadodiamide, the intact Gd complex found in Omniscan®) and Gd-DTPA-BMEA (gadoversetamide, the intact Gd complex found in OptiMARK®) have dissociation rate constants in plasma of $0.24\,d^{-1}$ and $0.17\,d^{-1}$, which translates into half-lives of 2.9 days and 4.1 days, respectively. For the Omniscan® and OptiMARK®, products with an excess ligand, these apparent constants are $0.0016\,d^{-1}$ and $0.0044\,d^{-1}$ ($t_{1/2}$ = 433 days and 157 days), respectively [5–11,16]. The intention of incorporating free ligand into the formulation is to improve safety, by decreasing the likelihood that free Gd will be released in the patient and bind to host anionic chemicals. In the presence of a non-physiological excess of phosphate used by Frenzel et al. to model hyperphosphatemia in end-stage renal disease, Omniscan®, and OptiMARK® have dissociation constants of $0.61\,d^{-1}$ and $0.42\,d^{-1}$ ($t_{1/2}$ = 1.1 d and 1.7 d), respectively [12,13,17].

The first aim of our study was to approximately identify the number of doses administered for Omniscan® and OptiMARK® and the number of cases of NSF associated with these agents to generate an incidence figure. The second aim of this paper was to explore the potential contribution of the amount of excess ligand added in the Omniscan® and OptiMARK® formulations on the incidence of NSF cases reported for these two agents.

2. Materials and methods

This study was designed as a retrospective cohorts observational study. The content of free ligand in the formulation was determined from the product inserts [14,18,19].

Estimation of the total number of doses administered for both agents since their approval for human use across multiple nations was determined based on data provided by the pharmaceutical companies. The number of unconfounded cases of NSF for these two agents was obtained from the previously published data, based on a legal database assessed from 1 January 2002 to December 2010 [20]. A separate analysis of a public adverse event database was performed to assess the impact of confounding on the results, and to determine if analyses from the legal database are generalizable to a broader set of patients. The potentially confounded cases of NSF were based on the number of cases reported to the FDA Adverse Event Reporting System (FAERS) from inception through 1 July 2015. To access FAERS reports, an open-source application-programming interface for FDA data known as "openFDA" was used. A query was run for all reports referencing only Omniscan® or OptiMARK®, and no other GBCA. The search included all events or was limited to adverse events (AEs) listed as "Nephrogenic Systemic Fibrosis". Only the exact phrase was used to narrow upon cases most strictly defined by the disease state under investigation rather than assigning a broad list of keywords potentially indicative of NSF (e.g., "fibrosis", "dermopathy" or "skin changes"). A preliminary search of the earlier name for the disease "nephrogenic systemic dermopathy" returned no AE reports. Duplicate event reports are excluded by the "count" procedure used in the openFDA query.

To estimate incidences and relative risks from adverse event data, several assumptions were made: that a vast majority of non-NSF reports would be AEs observed in clinical trials; that the proportion of AEs reported out of total AEs that occurred was the same for both Omniscan® or OptiMARK®; and that the true non-NSF AE rate is equivalent to what was observed in clinical trials. These assumptions facilitated the estimation of incidence and relative risk without using manufacturer estimates of total doses. The following mathematical consideration based on the OpenFDA query was applied:

$$\text{Total doses} = \frac{\text{Reported nonNSF AEs}}{(\text{Total nonNSF AEs/Total Doses})(\text{Reported nonNSF AEs}/\text{Total nonNSF AEs})}$$

The value of the expression is the numerator, and the parenthesized values in the denominator can be estimated from available data, allowing any reported event rate to be calculated from the number of reports for that event divided by the total number of doses estimated by this method. If the number of non-NSF adverse events per dose (Total non-NSF AEs/Total Doses) is the rate of AEs per dose in clinical trials (Clinical Trial AER), and the adverse event reporting rate (Reported non-NSF AEs/Total non-NSF AEs) is equivalent for Omniscan® and OptiMARK®, then the relative risk (RR) of reported NSF for Omniscan® compared to OptiMARK® is: $RR = \frac{\text{Reported NSF Omniscan} * (\text{Clinical Trial AER Omnican}) / \text{Reported nonNSF AEs Omniscan}}{\text{Reported NSF OptiMARK} * (\text{Clinical Trial AER OptiMARK}) / \text{Reported nonNSF AEs OptiMARK}}$.

The adverse event reporting rate (or reported fraction of adverse events) was assumed equivalent for Omniscan® and OptiMARK® because there is seemingly no compelling reason clinicians or others would be more likely to report adverse events as they occur with either agent. Since each FAERS report can contain multiple AEs for a single person, the non-NSF AE rate from clinical trials used the proportion of total patients who experienced AEs. AER from clinical trials were extracted from investigations in a variety of disease states (and healthy patients) and multiple regions to ensure generalizability with patients across the spectrum of current treatment; the clinical trial AERs were 8.4% for Omniscan® [21–26] and 28.3% for OptiMARK® [27,28].

A second FAERS analysis included other GBCAs that are associated with reports of NSF: Omniscan®, OptiMARK®, Magnevist®, MultiHance®, and ProHance®. As in the Omniscan®/OptiMARK® analysis, reports were only included if they implicated a single GBCA. The RR of a reported AE being for NSF was compared for each GBCA to Omniscan®, which did not require an estimate of total doses.

The incidence per million doses was approximated by the number of confirmed, unconfounded cases divided by the number of total doses administered (estimated by the manufacturer). For incidence estimates in the FAERs analysis, an alternative denominator estimated total doses by AEs reported and an assumed non-NSF AE reporting rate of 0.1%. RRs were calculated by division of incidence estimates (Omniscan® relative to OptiMARK®) and were tested for statistical significance by Chi-square test using a pre-defined alpha of 0.05. Bonferroni correction for multiple comparisons was used in the analysis of multiple GBCAs.

3. Results

Calculation of the content of free ligand shows that Omniscan® contains approximately 12 mg/mL excess ligand (+5 mol% caldiamide), whereas OptiMARK® is formulated with 28.4 mg/mL calversetamide (+10 mol%) [29].

The total estimated number of doses worldwide for Omniscan® and OptiMARK® based on manufacturer estimates were 87 million and 12 million doses respectively, which included doses administered in different countries irrespective of its date of approval. These estimates were provided by the manufacturers as of May 1, 2018.

The number of unconfounded cases of NSF due to Omniscan® reported on the legal database was 197 and for OptiMARK® 8 (Fig. 1). This rendered an incidence per million doses of 2.3 for Omniscan® and 0.7 for OptiMARK®, corresponding to an RR of 3.4 (95% CI 1.7–6.9).

The FAERs analysis found more reported NSF cases with Omniscan® compared to OptiMARK®, with magnitudes varying by the method used to estimate total doses given (Table 1). When incidences of NSF were calculated from manufacturer estimates of total doses, the relative risk of NSF with Omniscan® was 2.6 (95% CI 2.0–3.4), which was not significantly different from the estimate based on the unconfounded legal database. Both metrics that did not depend upon the manufacturer estimates indicated a 2-fold risk of reported NSF with Omniscan®; the method that calculated total doses from non-NSF adverse event rate found an RR of 1.6 (95% CI 1.2–2.1), which was also found as the RR of an AE report being for NSF 2.3 (95% CI 1.9–2.8). The effect of increased stability outweighed that of excess ligand in the comparison of Omniscan® NSF reports compared to those of other GBCAs (Table 2), with the RR increasing proportionately to the conditional stability of each ligand despite decreasing excess.

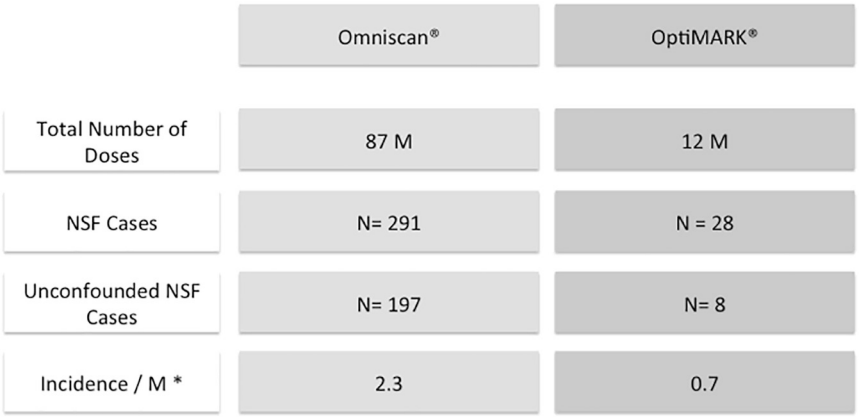

Fig. 1. Number of administered doses and cases of NSF (Omniscan® and OptiMARK®).
Note - M – million; N – number; NSF - Nephrogenic Systemic Fibrosis.
Estimation of the total number of doses was provided by the pharmaceutical companies (as of May 1, 2018).
The number of cases of NSF was reported on the legal database.
* Relative risk - 3.4 (95% CI 1.7–6.9).

4. Discussion

Our results showed that Omniscan® has a 3-fold increased incidence of unconfounded cases of NSF comparing with OptiMARK® with an incidence per million doses of 2.3 vs. 0.7 for Omniscan® and OptiMARK® respectively. The FAERs analysis of potentially confounded cases corroborated the 3-fold figure when manufacturer estimates of total doses were used, with incidence estimates increased to 13.1 and 5.0 per million doses of Omniscan® and OptiMARK®, respectively (~6–7 times as many cases per million doses than the unconfounded estimates). However, when the analysis used non-NSF error reports to estimate total doses or did not attempt to estimate total doses, a 2-fold increased risk was observed, with an inversely proportionate increase in incidence estimates (Table 1). The difference between the 3-fold and 2-fold estimates then is primarily the source of the total dose denominator; though the 2-fold figures overlap with the confidence intervals of the 3-fold estimates and thus may be considered lower limits of the present analyses, the potential for confounding and reporting biases obfuscating the FAERS analysis results should favor the legal database 3-fold estimate.

To our knowledge, this is the first study that shows a proportionally higher number of cases of NSF for Omniscan® than OptiMARK®, despite their comparable chemical properties. The explanation may be related to increased excess ligand present on OptiMARK®.

Since these agents have the weakest thermodynamic stability, it is conceivable that the free ligand may be essential to recapture the Gd atom before it becomes bound to host anionic chemicals (phosphates, carbonates, aminoglycans, etc.) [31–33]. Based on our results it appears that the amount of excess ligand seems of paramount importance for the relative risk of NSF when comparing two agents with very similar formulations and comparable thermodynamic stability.

The original decision to include excess caldiamide on Omniscan was based on a tendency of improving LD_{50} values as the mol% excess ligand increased, which was hypothesized to be the result of reduced Gd release [34]; computationally, it was expected that even 1% free ligand reduced Gd release by 80%, 5% excess reduced release by a further 85% (97% total reduction), and following their trend 10% excess would result in an over 99% reduction in Gd release compared with gadodiamide without excess [34].

Although the manufacturers may not have published peer-review explanations for the role of free ligands, proof of this importance can be derived from a study performed on a rodent model, by researchers from Bayer, unaffiliated with the manufacture of either Omniscan® or OptiMARK® [29].

Sieber et al. [29] evaluated macroscopic and histopathological skin changes in rats, following intravenous injection of Omniscan® and OptiMARK® formulated with 0%, 5%, and 10% excess ligand. They observed no significant differences between skin lesions and skin retention at the same amount of excess ligand. Skin changes appeared with formulations containing 0% free ligand (6/6) and with 5% excess ligand (3/6 and 4/6 for Omniscan® and OptiMARK®, respectively). No skin lesions neither histopathological findings were observed in animals treated with Omniscan® or OptiMARK® with 10% excess ligand. The researchers inferred that the excess ligand independently reduces retention in some compartments and may provide protective properties, presumably by scavenging released Gd, before it could result in toxic effects.

Similar to this animal study, our study that assessed almost the entire human clinical experience with Omniscan® and OptiMARK®, has shown that comparing these two chemical agents, the formulation which add more excess ligand, 10% versus 5%, was associated with a 3-fold decrease in the number of unconfounded cases of NSF. It may be not unreasonable to hypothesize that free ligand may offer this protective benefit not only in the original formulation but potentially also when administered subsequently, after the administration of the GBCA, to re-chelate Gd released in the body. This postulation is not straightforward. In an in vitro simulation analysis using a multicompartmental model, excess ligand had a strong effect on the amount of Gd retained

Table 1
Incidences and relative risks of Nephrogenic Systemic Fibrosis based on the FDA database analysis.

	Omniscan®	OptiMARK®	RR using manufacturer's estimates	RR using AE estimates	RR of report being NSF[b]
NSF reports, N (%)	1138 (70)	60 (31)			
Non-NSF reports, N (%)	477 (30)	135 (69)			
Rate per million manufacturer's estimated doses	13.1	5.0	2.6	1.6	2.3
Rate per million AE-estimated doses[a]	201	126	(CI 2.0–3.4)	(CI 1.2–2.1)	(CI 1.9–2.8)
			P < 0.0001	P < 0.001	P < 0.0001

P values based on Chi-square test.
Abbreviations: AE, adverse event; CI, 95% confidence interval; NSF, Nephrogenic Systemic Fibrosis; RR, relative risk.
[a] Based on an assumption of 0.1% total non-NSF AEs reported for both GBCAs: 5,650,065 Omniscan® doses and 476,972 OptiMARK® doses. The raw estimate is less relevant to the comparison then the relative amount of doses, which is ~10:1 Omniscan®: OptiMARK®, instead of ~7:1 as reported by manufacturer estimates.
[b] Relative risk of any given FAERS report being for NSF.

Table 2
The effect of physicochemical properties on the relative risk of a report for potentially confounded Nephrogenic Systemic Fibrosis compared to Omniscan®.

Comparator GBCA	$logK_{cond}$ pH 7.5	Excess ligand, mol%	NSF reports	Total reports	RR of NSF report*
OptiMARK®	15.0	10%	60 (31%)	195	2.3 (CI 1.9–2.8)
Magnevist®	17.7	0.2%	323 (7.6%)	4242	9.3 (CI 8.3–10.3)
ProHance®	17.1	0.1%	5 (1.4%)	367	51.7 (CI 21.6–123.6)
MultiHance®	18.4	0%	7 (0.4%)	1915	192.8 (CI 92.0–404.1)

* Listed as the unadjusted relative risk (RR) of an Omniscan® ($logK_{cond}$ 14.9, Excess ligand 5%) AE report being NSF compared to the index GBCA. All are significant with a P value of < 0.0001, which surpasses an adjusted alpha of $0.05/4 = 0.0125$ for multiple comparisons.

from a GBCA dose as the excess ligand slowed apparent elimination of Gd from the plasma, by retaining Gd in the blood and in rapid- turnover soft-tissue compartments, preventing "elimination" into other compartments. Nevertheless, the general linear model regression demonstrated that the percent of Gd retained is more influenced by renal function itself than excess ligand [35]. Although the majority of methodologies support a benefit of excess ligand further investigation is needed to validate real clinical benefit.

One undesirable effect of the extra ligand is the depletion of essential trace elements such as Zinc through transmetallation [29,31,36–40], which may be ameliorated by adding Zinc-bound ligand. In a preliminary report, intravenous calcium-/zinc-diethylene triamine penta-acetic acid (DTPA) administration in patients with normal renal function and previous gadolinium exposures was not associated with changes in serum values of Zn [41].

The strength of the present study is the enormous size of the data evaluated. There are however some important limitations. Among the most important is that the number of doses does not translate into the number of unique patients studied. Another limitation was the assumption of equivalent adverse event reporting rate (or reported fraction of adverse events) for both agents. However, this may have potentially caused bias resulting from media and literature coverage. Nevertheless, the agreement between cases in the legal database and those spontaneously reported provides some evidence that this bias does not fully explain our results. A number of patients would have undergone more than one GBCA-enhanced examination. Additionally, the market share information may have influenced the correlation million-doses/NSF-cases reported. Omniscan® has one of the largest market share (approved in 93 countries with 40 million administered doses) [20]. Since Omniscan® had been FDA-approved for triple dose studies, and OptiMARK® has also been employed off-label for high dose studies, and for a period between 2004 and 2006 both agents were used in substitute for iodine contrast, at high dose, at many centers in renal failure patients [42–45], there is no way to be sure how many unique patients received these agents. There is, however, no reason to suspect that the use of high dose studies would unduly bias against one or other agent, as likely both were used in multiple studies in the same individual or high dose studies in approximately the same fashion. Other major problems that stymy essentially all studies on NSF include: the issue of confounded use of multiple agents in the same individual; misidentifying agents used (and therefore misidentifying causative agent for NSF in those cases); underdiagnosis of NSF; dual-reporting of the same individual; and false positive and false negative histologic diagnosis of NSF [8]. Even the most accurate database (i.e., legal database) has limitations since only 3/4 of patients have biopsy-proven NSF. Taking all these issues into consideration, compensation for this was offset by studying vast numbers and accessing many databases to establish the numbers generated in our study. In an attempt to compensate for this, we performed two different analyses, using data from different sources (legal database and the openFDA query) with similar results. The FAERS analysis revealed a reporting bias for NSF relative to other AEs, which does not correlate with the prevalence of each. NSF appears to have a much higher proportional reporting ratio than more common, non-specific AEs. The FAERS analysis may have also been biased by the amount of attention given to the specific association between Omniscan® and NSF, and may have increased reporting or (mis)diagnosis of NSF in patients who received that drug (or misattribution of NSF to Omniscan® as a catch-all GBCA when records are not available), relative to the other agents. As such, any analysis of AE reports adjusted for total reports or doses may merely be an indirect measure of how much attention each agent has received from the media, scholarly works, and regulatory agencies. Finally, we believe that a more thorough FAERS analysis could be performed using logistic regression, patient factors in the FDA reports and all available GBCAs considering other potentially essential formulation parameters to determine the independent impact of each factor on the relative reporting rate of NSF. In fact, the analysis including multiple contrast agents suggested an incidence trend that depends on both excess ligand and conditional stability.

In conclusion, our findings emphasize the importance of free ligand in agents with lower thermodynamic and kinetic stability and suggest that the amount of excess ligand might be associated with the relative risk of NSF; nevertheless, more data is needed to investigate this association and potential confounders not addressed in the current analysis.

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