# The Impact of Excess Ligand on the Retention of Nonionic, Linear Gadolinium-Based Contrast Agents in Patients With Various Levels of Renal Dysfunction: A Review and Simulation Analysis

John P. Prybylski and Michael Jay

**The role of gadolinium (Gd)-based contrast agents (GBCAs) in the pathophysiology of nephrogenic systemic fibrosis (NSF) is now uncontested. Although the definitive mechanism has not been established, the association with weaker GBCA ligands and with reduced renal clearance supports a hypothesis that Gd release from the GBCAs is a key process in precipitating the disease. Prevention strategies often include the use of more stable GBCA ligands in patients with reduced kidney function, but animal models and some clinical data suggest that better patient outcomes can be achieved when excess ligand is administered with weaker GBCAs; this is particularly significant for OptiMARK, which contains a nonionic, linear ligand similar to gadodiamide, the active ingredient in Omniscan, but contains twice the amount of excess ligand. Here we review evidence regarding the use of OptiMARK over Omniscan for prevention of NSF and perform a pharmacokinetic-based simulation to determine if the presented evidence is consistent with the established kinetics of GBCAs and Gd.**

**Key Words:** Gadolinium, Nephrogenic systemic fibrosis, Gadodiamide, Gadoversetamide, Kinetics

## INTRODUCTION

The use of gadolinium (Gd)-based contrast agents (GBCAs) for magnetic resonance imaging has recently been associated with several clinical controversies, all of which relate to the chemical and pharmacologic kinetics of these agents. In patients with normal renal function, Gd has been found deposited in the brain,[1] bone,[2] and skin[3,4] and to be present in urine collections years after the GBCA should have been completely cleared, sometimes associated with painful and disorienting symptoms.[5,6] Similar skin retention has been observed in patients with severely reduced renal function but to a greater extent and strongly associated with nephrogenic systemic fibrosis.[7,8] Retention and its outcomes in all patients is independently associated with the thermodynamic and kinetic stability of GBCAs,[9-11] resulting in a common hypothesis that the outcomes are associated with the release of Gd.[10] Because GBCAs are cleared by the kidneys,[12] the obvious result of slowed clearance is greater residence time of the GBCAs in patients with renal dysfunction and thus facilitating greater release of Gd.

In terms of both thermodynamic and kinetic stability of GBCAs, the nonionic, linear contrast agents (eg, gadodiamide) rank lowest and macrocyclic contrast agents (eg, gadoterate) rank highest.[13,14] This demonstrates a theoretical benefit of macrocyclic agents, which is corroborated by clinical outcomes data.[15] Thus, policies seeking to reduce the incidence of nephrogenic systemic fibrosis (NSF) in populations focus on using more stable agents in patients with renal dysfunction.[16] But are there other approaches that do not eliminate the role of nonionic formulations, such as Omniscan (gadodiamide with 5 mol% caldiamide)[17] and OptiMARK (gadoversetamide with 10 mol% calversetamide)[18]? Are both agents associated with equally high risk or does the 5% difference in the amount of excess calcium-associated ligand make a clinically relevant difference? Here we review *in vitro*, preclinical and clinical evidence for or against the use of OptiMARK over Omniscan in patients with reduced renal function and present a simulation-based analysis to determine if the physiological and chemical kinetics of GBCAs can explain any observed differences in OptiMARK and Omniscan outcomes.

### *In Vitro* Data

All kinetic studies are based on measurable rates, and the chemical kinetics of GBCA stability can be defined by the rates of 2 reactions: dissociation and association of Gd and ligand. The rate of association is first order with respect to Gd and ligand concentrations, and the rate of dissociation is first order with respect to GBCA concentration. Thus, when a GBCA is present in solution with no other ligand or Gd, dissociation is the favored reaction; any excess ligand in solution slows dissociation by increasing the rate of the reverse reaction. Both Omniscan and OptiMARK are formulated with excess ligand, but at only 5% and 10% the molar concentration, respectively, which would presumably have a marginal effect on release of Gd *in vivo*. Based on early literature from the inventors of Omniscan, the decision to include excess caldiamide was based on a trend of improving $LD_{50}$ values as the mol% excess ligand increased, which was hypothesized to be the result of reduced Gd release[19]; computationally, it was expected that even 1% free ligand reduced Gd release by 80%, 5% excess reduced release by a further

*From Division of Pharmacoengineering and Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC.*

*Financial Disclosure: The authors have no relevant financial disclosures.*

*Address correspondence to John P. Prybylski, PharmD, Division of Pharmacoengineering and Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, University of North Carolina, 4012 Marsico Hall, Chapel Hill, NC 27599-7362. E-mail: jprybylski@unc.edu*



*1548-5595/$36.00*
*http://dx.doi.org/10.1053/j.ackd.2017.03.002*

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. An *in vitro* analysis of Gd release from various GBCAs in human serum corroborated the reaction rate hypothesis in that Gd dissociated from OptiMARK and Omniscan dissociated slower than gadodiamide and gadoversetamide, but OptiMARK and Omniscan did not release significantly different amounts of Gd.[14] When release was stimulated by excess phosphate, release rates and amounts were approximately the same among OptiMARK, Omniscan, gadodiamide, and gadoversetamide. Thus, *in vitro* kinetic analyses do not support a conclusion that 10% excess is any different from 5% excess and that strong competing reactions for Gd neutralize any effect from excess.

Fibroblast stimulation has been developed as an important *in vitro* model to assess how GBCAs contribute to the pathology of NSF.[20] One study compared the proliferation of fibroblasts from control and NSF patients incubated in different classes of GBCAs, including gadodiamide with or without excess caldiamide and gadoversetamide without excess calversetamide.[21] In control patients, there was more proliferation with gadodiamide + caldiamide and gadoversetamide alone than gadodiamide alone, but in NSF patients gadodiamide alone was more proliferative than gadoversetamide, and both more so than gadodiamide + caldiamide. In general, the more stable ionic, linear GBCAs induced more fibroblast proliferation than the nonionic, linear GBCAs, which induced more proliferation than the most stable macrocyclic GBCAs in control patients; a more intuitive trend of more proliferation with decreasing stability was observed in NSF fibroblasts. The observed differences between gadodiamide and gadoversetamide and the inversion of excess ligand trend in control and NSF fibroblasts suggest that thermodynamic and kinetic stability would not be the exclusive cause of clinical outcome differences and may perhaps be a minor factor.

**CLINICAL SUMMARY**

- *In vitro* cell culture work, animal models, and Food and Drug Administration error reports suggest OptiMARK is safer than Omniscan with regard to induction of nephrogenic systemic fibrosis, but these findings suggest highly variable magnitudes of effect (ie, true reduced risk of nephrogenic systemic fibrosis in using OptiMARK rather than Omniscan) and are limited by methodologies.
- Chemical kinetics do not support a difference between Omniscan and OptiMARK.
- A multicompartmental model of GBCAs and Gd allowing reversible chelation can simulate observations in patients well and suggest that Gd release from the GBCAs dictates the long-term retention in patients.
- The simulation predicts that excess ligand can reduce Gd retention, but the reduction is not clinically significant, not as impactful as kidney function and of more relative importance in non-ESRD patients.

## Preclinical Models

Bayer Schering Pharma, the manufacturer of the linear, ionic GBCA Magnevist (gadopentetate with 0.2% molar excess of diethylenetriaminepentaacetic acid [DTPA]), Eovist (gadoxetate), and the macrocyclic, nonionic GBCA Gadavist (gadobutrol) has performed some of the most extensive rodent studies of NSF induction from different GBCA classes and formulations.[22] Most of their work used healthy rats administered high daily doses of Gd formulations over a prolonged period to model the slowed clearance in patients with renal impairment[23-26] but observed similar trends in nephrectomized rats.[27] In each study, they report macroscopic and microscopic skin lesion trends, and skin concentrations of Gd, which in all cases demonstrate a positive correlation (ie, the greater skin concentration of Gd, the more lesions observed). In several studies, Omniscan was compared with gadodiamide alone,[23,26] or OptiMARK,[24-27] and in those cases, there was an intuitive inverse correlation between excess ligand and skin concentration of Gd. In a key analysis, gadodiamide and gadoversetamide with 0, 5, and 10 mol% calcium ligand were administered.[26] No significant differences were observed between the skin retention of each agent at the same amount of excess ligand, and the number of lesions was essentially the same (6/6 for 0 mol%, 3-4/6 for 5 mol%, and 0/6 for 10 mol%). This work supports a conclusion that excess ligand independently reduces retention in some compartments, but the mechanism is uncertain based on the *in vitro* work from Bayer which demonstrated no difference in OptiMARK and Omniscan Gd release rate and amount.[14] This suggests that the pharmacokinetics of GBCAs, Gd, and ligand are responsible for observed differences but is the magnitude of difference expected to be the same in clinical situations? The rats were given ~5× the body surface area-based human-animal dose conversion recommended by the Food and Drug Administration (FDA) (0.6 mmol/kg)[28] daily for 4 weeks. If the hypothesized mechanism is reducing Gd release with excess ligand, administering an excessively high dose (which was used to improve detection) would poorly simulate a normal dose because Gd acetate pharmacokinetics in some compartments are known to be dose dependent.[29] Additionally, there was no assessment to determine if the rats continued to have normal renal function despite the fact that GBCAs have been associated with nephrotoxicity (although the association is stronger for ionic agents)[30]; it is also known that high doses of Gd acetate in male rats is associated with a biomarker of renal dysfunction (blood urea nitrogen),[31] which implies that release from GBCAs would magnify any observed retention in male rats because it would itself reduce clearance, thus making these high, sequential dosing models overpowered for minor differences.

## Clinical Evidence

There is minimal clinical evidence directly comparing the different outcomes in human patients given Omniscan or OptiMARK. In clinical trials for a variety of indications, Omniscan is associated with adverse events in 8.4% of patients,[32-36] whereas adverse events occur in 28.3% of