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Feature Article

Novel sorbents for removal of gadolinium-based contrast agents in sorbent dialysis and hemoperfusion: preventive approaches to nephrogenic systemic fibrosis

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Abstract

Many forms of organocomplexed gadolinium (Gd) contrast agents have recently been linked to a debilitating and a potentially fatal skin disease called nephrogenic systemic fibrosis (NSF) in patients with renal failure. Free Gd released from these complexes via transmetallation is believed to be the most important trigger for NSF. In this work, nanostructure silica materials that have been functionalized with 1-hydroxy-2-pyridinone (1,2-HOPO-SAMMS) have been evaluated for selective and effective removal of both free and chelated Gd (gadopentetate dimeglumine and gadodiamide) from dialysate and blood. 1,2-HOPO SAMMS has high affinity, rapid removal rate, and large sorption capacity for both free and chelated Gd, properties that are far superior to those of activated carbon and zirconium phosphate currently used in the state-of-the-art sorbent dialysis and hemoperfusion systems. The SAMMS-based sorbent dialysis and hemoperfusion will potentially provide an effective and predicable strategy for removing the Gd from patients with impaired renal function after Gd exposure, thus allowing for the continued use of Gd-based contrast magnetic resonance imaging while removing the risk of NSF.

From the Clinical Editor: Chelated gadolinium (Gd) contrast agents have been linked to a debilitating disease called nephrogenic systemic fibrosis (NSF) in patients with renal failure. Free Gd^{+3} released from the contrast agents is believed to be the trigger for NSF. In this work, functionalized nanostructured silica materials were evaluated for removal of both free and chelated gadolinium both from dialysate and blood. The new method demonstrated a rapid removal rate and large sorption capacity, and overall was far superior to currently used state-of-the-art sorbent dialysis and hemoperfusion systems.

Key words: Contrast agent; Gadolinium; Hemoperfusion; Hydroxyl pyridinone; NSF; SAMMS; Sorbent dialysis

Gadolinium (Gd)-based contrast agents are used to enhance the visibility of internal structures when patients undergo magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). The Gd-based contrast agents have recently been linked to a debilitating and a potentially fatal skin disease called nephrogenic systemic fibrosis (NSF) in patients with renal failure.[1,2] NSF is often described as a swelling and tightening of the skin of extremities and weakness of muscles, thus limiting the ability of patients to move.[3] NSF may also affect internal organs, such as lungs and heart, which may lead to death.[4] Currently, there is no effective treatment for NSF once it is manifest. In May 2007, the U.S. Food and Drug

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Administration (FDA) requested a boxed warning of all Gd-based contrast agents to inform consumers about the risk of developing NSF in patients with severe kidney insufficiency, in liver transplant patients (both before and after), or in those with chronic liver diseases.[5] This warning affects a large number of patients (eg, an estimated 27.5 million MRI procedures were performed in 2007 in the United States alone, and 43% used Gd-based contrast agents as part of the imaging procedure[6]). When possible, use of Gd-based contrast agents should be avoided in patients with renal failure. Determination of which imaging diagnostic approach to use is difficult when the kidney functions of the patients are unknown. There are a number of conditions where alternative imaging methods such as computed tomography (CT) or unenhanced MRI cannot replace Gd-enhanced MRI in diagnostic power. Lastly, CT with iodinated enhancement is a risk factor in patients with preexisting azotemia.[7] If Gd use is unavoidable, hemodialysis should be administered promptly afterward to facilitate clearance of the Gd contrast agents. The efficiency of Gd clearance by dialysis has not been widely studied. Some studies suggest that 65% to 78% of Gd contrast could be cleared after one hemodialysis session and 98% after three sessions.[8-10] However, proof of dialysis efficacy is lacking as assumptions regarding Gd removal from the body are based on plasma decay curves, which overestimate the effectiveness of hemodialysis clearance of Gd.[11] Delayed clearance (eg, delayed hemodialysis after patients receive contrast agents) would prolong the duration of exposure to Gd-based contrast agents, which could lead to higher risk of developing NSF.[12]

This is a medical issue where advanced nanostructure materials, by virtue of their high surface area and chemically selective functionality, can make a positive impact. This work evaluates a new sorbent material, the self-assembled monolayers on mesoporous silica supports (SAMMS Steward Advanced Materials, Chattanooga, Tennessee), to be used in sorbent dialysis and in hemoperfusion as alternative means for effective and rapid clearance of Gd-based contrast agents. Sorbent dialysis exploits the sorbent cartridge that makes the system both simple and regenerative, unlike conventional hemodialysis. Spent dialysate from a dialyzer flows through the sorbent cartridge where the waste is removed and the regenerated dialysate is recirculated. Thus, the sorbent dialysis system is simpler, generates less waste, and is more portable than the conventional hemodialysis system. Sorbent dialysis consumes less power because there is no need to purify and sterilize tap water used to make the dialysate. There is also no need for dialysis machines to pump and heat large volumes of dialysate. To make the sorbent dialysis work for Gd clearance, sorbent must have high affinity, rapid removal rate, and sufficient sorption capacity for Gd in the dialysate. The state-of-the-art sorbent cartridge still relies on activated carbon and zirconium phosphate for removal of metal cations. Functional nanomaterials offer the ability to tailor the three-dimensional architecture, the pore size, and the interfacial chemistry in ways that traditional sorbents like activated carbon cannot. This work shows that ordered mesoporous silica that is functionalized with suitable organic ligands offers much superior sorption properties for Gd-based contrast agents than that of the currently used materials. The feasibility of using this material in hemoperfusion of Gd-based contrast agents is also evaluated.

Methods

Sorbent materials

Synthesis and characterization of mesoporous silica functionalized with acetamide phosphonic acid (AcPhos),[13,14] di-phosphonic acid (Di-Phos), and three variations of hydroxyl pyridinone (HOPO) ligands[15,16] were described in our previous work. Figure 1 shows the chemical structures of the ligands of SAMMS. For comparison, high-surface-area activated carbon (Darco KB-B; Sigma-Aldrich St. Louis, Missouri) and zirconium phosphate cation exchange resins (3M Company, St. Paul, Minnesota), both typically used for removing metal cations in sorbent dialysis systems, were also tested along with the SAMMS materials.

SAMMS for sorbent dialysis

For evaluation of SAMMS for potential use in sorbent dialysis, two test matrices were studied. The first matrix was a dialysate (PrismaSate, BGK4/2.5) purchased from Gambo Inc. (Lakewood, Colorado) that consists of 2.5 mEq/L Ca^{2+}, 1.5 mEq/L Mg^{2+}, 140 mEq/L Na^{+}, 4 mEq/L K^{+}, 113 mEq/L Cl^{-}, 3 mEq/L lactate, 32 mEq/L HCO_3^{-}, 110 mg/dL glucose, and osmolarity of 300 mOSm/L. The second matrix was 0.1 M NaCl, which was adjusted with 0.1 M HCl to the desired pH values (eg, from pH 2.5 to 6.0). Two forms of Gd were studied: inorganic or free Gd (from Gd atomic absorption standard solution consisting of 1000 mg/L Gd^{3+} in 1% HNO_3; Sigma-Aldrich) and chelated Gd including gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals Inc., Montville, New Jersey) and gadodiamide (Omniscan; GE Healthcare Inc., Princeton, New Jersey). The Gd species were spiked to the test matrices and incubated for 30 minutes prior to a batch sorption experiment.

K_d measurements

For the K_d measurements, the dialysate was spiked with free Gd^{3+} solution to obtain ~100 μg/L. After 30 minutes of incubation, it was aliquoted into 10 mL volumes in a 20-mL polypropylene vial containing 0.002 g solid sorbent [liquid per solid (L/S) ratio of 5000 mL/g]. The sample was then shaken for 2 hours at 160 rpm on an orbital shaker. After 2 hours, the solution was removed by filtering thru 0.20-μm Nylon-membrane syringe filters, and the filtrate was kept in 1 vol% HNO_3 prior to metal analysis. The concentrations of Gd in solutions before and after being contacted with a sorbent material were analyzed using an inductively coupled plasma–mass spectrometer (ICP-MS; Agilent 7500ce, Agilent Technologies, Santa Clara, California). Similar experiments were performed with gadopentetate dimeglumine in pH-adjusted 0.1 M NaCl solutions and gadodiamide in dialysate. All batch experiments were performed in triplicate and the averaged values were reported.

Sorption capacity

The Gd sorption capacity of each sorbent material was measured in the same fashion as with the K_d. Free Gd and chelated Gd concentrations in solutions were varied until maximum sorption capacity was obtained. At any data point, Gd was used in large excess of the number of binding sites to ensure that saturation adsorption was obtained (eg, 0.1 to 1 mg/L

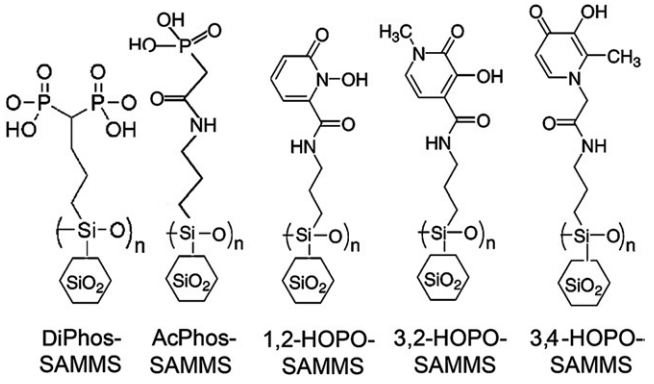

Figure 1. Chemical structures of SAMMS ligands.

free Gd^{3+} at L/S of 100,000 mL/g or 0.1 to 2 mg/L chelated Gd at L/S of 50,000 mL/g).

Sorption kinetics

The kinetics of Gd sorption was performed in the same fashion as the equilibrium study except that 1 mL of well-mixed aliquot was removed and filtered at 1, 2, 5, 10, 30, 60 minutes, 2, 8, and 24 hours, and the initial solution volume was increased to 50 mL to minimize the change in L/S ratio.

Regeneration

Seven cycles of Gd adsorption and regeneration of 1,2-HOPO-SAMMS were performed to assess the ability of SAMMS to be regenerated and its effectiveness after the regeneration. For the adsorption step, 10 mL 100 μg/L Gd^{3+} in dialysate was passed through the bed of 0.01 g 1,2-HOPO-SAMMS at a flow rate of 1.5 mL/min, and the filtrate was collected for Gd and Si analysis. Next, 40 mL deionized (DI) water was passed through the bed to remove the residual unadsorbed Gd. For the regeneration step, 10 mL 0.5 M HCl was passed through the bed at 1.5 mL/min, and the filtrate was collected for Gd and Si analysis. Next, 40 mL DI water was passed through the bed to remove the residual acid. The adsorption and desorption steps were repeated on the same SAMMS bed for the total of seven cycles.

SAMMS for hemoperfusion

For evaluation of SAMMS for hemoperfusion of Gd-based contrast agent, blood from two sources was used. For the first source, human blood and plasma were purchased from Golden West Biologicals, Inc. (Temecula, California). They were spiked with known amount of free Gd^{3+} and gadodiamide prior to batch sorption with SAMMS. The second source of blood was collected from a rat at 10 days after the animal was intravenously injected with 2.5 mmol gadodiamide/kg body weight. Before injecting with gadodiamide, 8-week-old, male Wistar rat was induced with chronic kidney disease by daily feeding with 0.75% adenine per weight of food for 4 weeks.[17] The rat blood having 1.4 mg Gd/L (measured by ICP-MS) was then subjected to batch adsorption with SAMMS. Adsorption experiment was performed using the following conditions: 0.01 g SAMMS in 1 mL fluid, shaken for 1 hour at 160 rpm and 37°C. Then the sorbent was removed, and the Gd content in the fluid before and after adding the sorbent was analyzed using the ICP-MS. The experiments were conducted in replicate, and the average value of percentage Gd removal from the liquid phase was reported. Studies on humans and animals (rodent) were approved by the institutional review committee of PNNL, and the procedures followed were in accordance with institutional guidelines. Animals were treated humanely. The use of commercially available human blood fell under exempt classification.

Table 1
The K_d of various sorbent materials for Gd^{3+} and gadopentetate Gd

Sorbent	K_d of Gd^{3+} (mL/g)[a]	K_d of gadopentetate Gd (mL/g)[b]
Activated carbon	1,500	3,600
Zirconium phosphate	190	250
AcPhos-SAMMS	44,000	16,000
1,2-HOPO-SAMMS	7,200,000	450,000
3,2-HOPO-SAMMS	5,600,000	13,000
3,4-HOPO-SAMMS	11,000,000	1,200

[a] Measured in dialysate (pH 8.0), initial [Gd^{3+}] of 100 μg/L, L/S of 5000 mL/g.

[b] Measured in 0.1 M NaCl (pH 3.5), initial [gadopentetate Gd] of 50 μg/L, L/S of 5000 mL/g.

Results

At the present time, the most important trigger for NSF is believed to be the free Gd, which is released from the Gd-based contrast agents (in various forms of Gd complexes) by transmetallation, a process in which Gd is replaced by other ions, such as iron, zinc, or copper.[18-21] If the Gd complex could be removed immediately after the imaging study, it would prevent the dissociation of Gd and should eliminate NSF as a complication. If not, it would be desirable to remove both the free and chelated Gd. The properties of sorbent materials for the removal of both free Gd and chelated Gd from dialysate (aimed to be used in sorbent dialysis) and from blood (aimed to be used in hemoperfusion) were evaluated as follows.

Adsorption affinity

The affinity of a sorbent for a target species was frequently represented with the distribution coefficient (K_d; mL/g), which is simply a mass-weighted partition coefficient between the solid phase and liquid supernatant phase as follows:

$$K_d = \frac{(C_o - C_f)}{C_f} \times \frac{V}{M} \quad (1)$$

where C_o and C_f are the initial and final concentrations of the target species in the solution, determined by ICP-MS; V is the solution volume in milliliters; and M is the mass in grams of the sorbent. In general, K_d values of $\sim 10^3$ mL/g are considered good and those above 5×10^4 mL/g are outstanding.[13]

There are many forms of Gd complexes currently used as contrast agents. The charge and structure of Gd complexes are believed to correlate with the triggering of NSF: Non–ionic-charged, linear-structured, Gd-based contrast agents (eg,

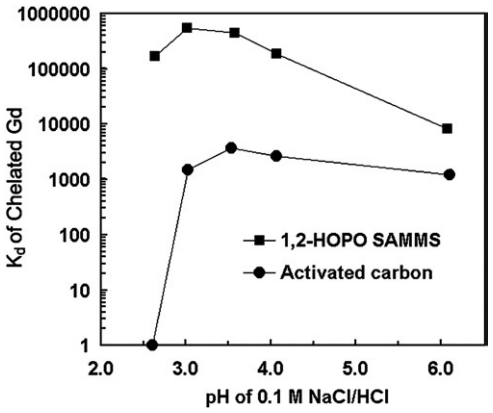

Figure 2. Distribution coefficients of gadopentetate Gd measured on 1,2-HOPO-SAMMS and Darco KB-B activated carbon in pH-adjusted 0.1 M NaCl, initial [gadopentetate Gd] of 50 ppb and L/S of 5000 mL/g.

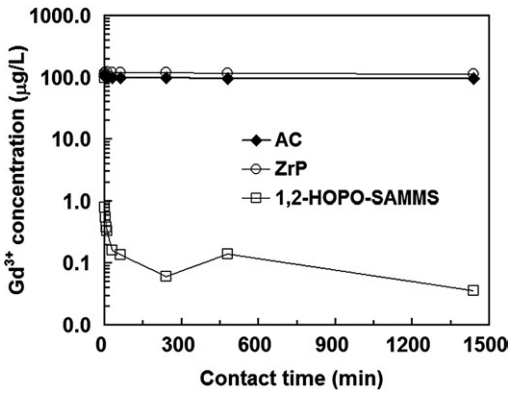

Figure 3. Adsorption kinetics of Gd^{3+} measured on 1,2-HOPO-SAMMS, activated carbon (AC), and zirconium phosphate (ZrP) in dialysate (pH 8.0), initial [Gd^{3+}] of 100 μg/L, L/S of 5000 mL/g.

gadodiamide, gadoversetamide) are more likely to cause NSF than are cyclical structured, Gd-based contrast agents (eg, gadoteridol, gadobutrol, gadoterate meglumine), and those ionic-charged, linear-structured, Gd-based contrast agents (eg, gadopentetate dimeglumine, gadobenate dimeglumine) are in between with regard to risk of triggering NSF.[22] As of June 2007, 180 worldwide cases of NSF have been associated with gadodiamide, 78 cases have been associated with gadopentetate dimeglumine, and no case has been associated with cyclical structured contrast agents.[22] In this work, gadodiamide and gadopentetate dimeglumine were selected for the study because they are most commonly used and have been linked to most NSF cases.

Table 1 shows the affinity (K_d) of various sorbents for free Gd in a representative dialysate. Note that "free Gd" refers to Gd^{3+} that was added to the solution, but in carbonate-rich, alkaline solutions (eg, dialysate), Gd is likely to form anionic carbonate complexes.[23] The K_d values suggest that the three analogues of HOPO-SAMMS are outstanding sorbents (K_d ~10^6 to 10^7) for removing "free Gd" and are substantially better than the activated carbon (K_d ~10^3) and zirconium phosphate (K_d ~10^2). Rare

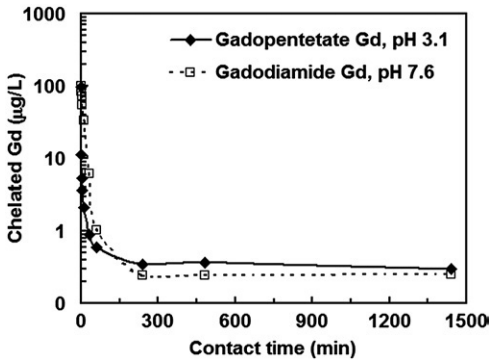

Figure 4. Adsorption kinetics of gadopentetate Gd and gadodiamide Gd measured on 1,2-HOPO-SAMMS, initial [chelated Gd] of 100 μg/L, L/S of 5000 mL/g.

earth cations like Gd are hard Lewis acids and are considerably larger than the typical transition-metal cations, thus both hard anionic ligands and ligand synergy are important attributes in designing effective complexing agents for the rare earth metals.[16] The HOPO are hard ligands and highly selective f-block chelators (inspired by iron-binding siderophores from bacteria[24]). Even in large excess of other cations in dialysate (eg, 2000 mol Ca, 1200 mol Mg, 22,000 mol Na, and 6300 mol K per mol Gd), the ligands are still very selective for the lanthanide Gd. On the silica substrate of SAMMS, the HOPO ligands are in relatively close proximity, allowing multiple ligand-metal interactions and strong binding affinity.[15] In comparison, 1,2-HOPO-SAMMS offers two and three orders of magnitude higher K_d for Gd than those of activated carbon and zirconium phosphate, respectively (Table 1). Unlike the multidentate ligands of SAMMS, the ligands of the activated carbon (eg, carboxyls, phenols)[25] undergo a less ordered, more random coordination with Gd species.

Furthermore, 1-2-HOPO-SAMMS also had high affinity for gadodiamide Gd in dialysate with the K_d value of 2,000,000 (measured at initial gadodiamide Gd of 100 μg/L and L/S of 5000). However, no materials tested could capture gadopentetate Gd from the dialysate (pH ~8), perhaps due to the strong bonding between Gd^{3+} and diethylene triaminepenta acetic acid (DTPA). Thus, to find out at what pH the Gd could dissociate from gadopentetate dimeglumine and be captured by SAMMS materials, we have conducted the pH isotherm on 1,2-HOPO-SAMMS using pH adjusted 0.1 M NaCl solutions. Figure 2 shows the K_d of gadopentetate Gd measured on 1,2-HOPO-SAMMS and activated carbon in pH-adjusted 0.1 M NaCl. The K_d value on 1,2-HOPO-SAMMS was 8300 at pH 6.0 and increased to 550,000 as the pH decreased to 3.0, suggesting more Gd dissociated from the Gd complex and bound to the SAMMS with decreasing pH. As the pH decreased from 3.0 to 2.5, the K_d dropped from 550,000 to 170,000, suggesting less Gd adsorption perhaps due to increased protonation of 1,2-HOPO-SAMMS. As dissociation of Gd from the chelate followed by the deposition of the free Gd in tissues is believed to trigger NSF, the data in Figure 2 provide a useful insight into the pH where the bond between Gd and DTPA is weakened (which has not been easy to measure because standard mass spectrometry only gives the total

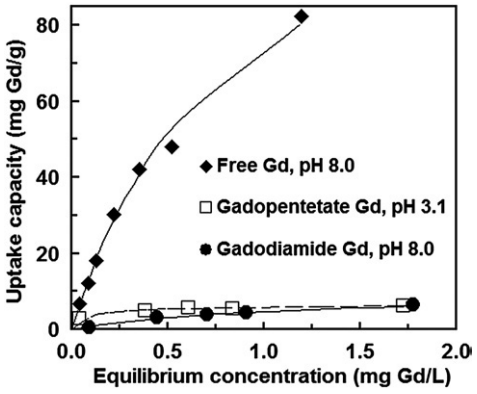

Figure 5. Adsorption isotherm of free Gd in dialysate (pH 8.0, L/S 100,000 mL/g), gadopentetate Gd in 0.1 M NaCl (pH 3.1, L/S 50,000 mL/g), and gadodiamide Gd in dialysate (pH 8.0, L/S 50,000 mL/g) measured on 1,2-HOPO-SAMMS.

Gd content and not dissociated Gd content). At optimal pH 3.5, no other sorbents could capture gadopentetate Gd as effective as 1,2-HOPO-SAMMS, as indicated by the lower K_d values in Table 1. However, lowering the dialysate pH to remove gadopentetate Gd is doable but not very practical, thus to remove chelated Gd directly from the dialysate, SAMMS with other functional groups must be developed. Nevertheless 1,2-HOPO-SAMMS has outstanding affinity for removing both free and gadodiamide Gd from dialysate (the latter linked to most NSF cases) thus was chosen for further evaluation.

Adsorption kinetics

The efficiency and the speed of the Gd removal are critical to sorbent dialysis for preventing tissue deposition of Gd. Figure 3 shows the kinetics of free Gd removal from dialysate with 1,2-HOPO-SAMMS, activated carbon, and zirconium phosphate, and Figure 4 shows the kinetics of gadodiamide removal from dialysate (pH 7.6) and gadopentetate Gd removal from 0.1 M NaCl (pH 3.1) with 1,2-HOPO-SAMMS. The time to reach 50% removal ($T_{1/2}$) was 0.14 minute for free Gd in dialysate, 4.2 minutes for gadodiamide Gd in dialysate, and 0.3 minute for gadopentetate Gd in sodium chloride (pH 3.1). About 99% of free Gd was removed by 1,2-HOPO-SAMMS in 1 minute, 95% of gadopentetate Gd was removed in 2 minutes, and 95% of gadodiamide Gd was removed in 30 minutes. This rapid removal rate is attributed to the rigid and parallel-pore structure and suitable pore size (~6.0 nm) of the SAMMS material. Our test was done with low Gd content (eg, 100 μg/L), but in practice, the dialysate Gd content is normally higher. For example, when the dialysis was applied at 1 hour, 2 hours, and 3 hours after the injection of 0.1 mmol gadodiamide per kilogram body weight to 10 patients, the mean dialysate Gd level was about 95, 70, and 45 mg/L, respectively.[26] When the dialysate Gd content is higher, the kinetics will be faster due to lower mass transport resistance, and the high percentage of removal can be achieved by increasing sorbent per liquid ratio (to be higher than 0.2 g/L as in our test). Even at low dialysate Gd content of 100 μg/L, activated carbon and zirconium phosphate could remove 15% and 7% of free Gd, respectively. Note that the low removal percentages is mainly attributed to the low affinity (K_d) and not the slow rate. Based on the K_d values in Table 1, activated carbon should remove a similar amount (eg, 15%) and zirconium phosphate. The greater efficacy of SAMMS over activated carbon or zirconium phosphate will require much smaller sorbent, thus enabling compactness and miniaturization of the dialysis devices, which is necessary for the development of the next generation (personal and portable) of dialysis systems.

Table 2
The K_d of Gd^{3+} measured after passing 10 mL dialysate containing 100 μg/L Gd^{3+} through 0.01 g 1,2-HOPO-SAMMS at a flow rate of 1.5 mL/min (sorption step), followed by 10 mL 0.5 M HCl at 1.5 mL/min after each sorption step

Cycle	Final [Gd^{3+}] (μg/L)	K_d (mL/g)
1	4.2	22,000
2	5.4	17,000
3	4.4	21,000
4	4.7	20,000
5	4.9	19,000
6	3.8	24,000
7	3.8	25,000

Adsorption capacity

Large surface area (900 m^2/g) of the mesoporous silica results in large ligand loading capacity (0.5 to 1.0 HOPO-silane/nm^2)[15] and consequently large metal loading capacity even in high salt content dialysate. Figure 5 shows the adsorption isotherms of free Gd and gadodiamide Gd in dialysate (32 mM HCO_3^-, pH 8.0) and gadopentetate Gd in 0.1 M NaCl (pH 3.1), measured on 1,2-HOPO-SAMMS. At the sorption capacity of 82 mg of free Gd/g SAMMS (last data point), 40% of 2 ppm Gd was removed using only 0.01 g SAMMS/L dialysate (L/S of 100,000 mL/g). Increased amount of SAMMS material would achieve higher percentage removal. All isotherm data sets can be fitted to the Langmuir adsorption model, which is given by

$$Q_e = \frac{Q_{\max} K_L C_e}{1 + K_L C_e} \quad (2)$$

where Q_{max} is the adsorption capacity (mg metal ion/g sorbent) when all adsorption sites are occupied, C_e is the equilibrium concentration of the metal ion, and the Langmuir constant K_L (L solution/mg metal ion) represents the ratio of the adsorption rate constant to the desorption rate constant. The maximum adsorption capacity (Q_{max}) was estimated to be 135 mg free Gd, 10.3 mg gadodiamide Gd (equivalent to 37 mg gadodiamide), and 6.4 mg gadopentetate Gd (equivalent to 38 mg gadopentetate dimeglumine) per gram 1,2-HOPO-SAMMS. The good agreement between the data and Langmuir adsorption model (eg, linear fit correlations: R^2 >0.96 for free Gd and >0.99 for both chelated Gd) implies that the adsorption of both free and chelated Gd onto the SAMMS material occurred as a single monolayer and was uniformly distributed across the sorbent surface, not nucleating or precipitating out of solution.

Regeneration

SAMMS has a median particle size of 20 μm, which makes the material suitable for flow systems (engineered forms to

Table 3
Removal of 1 mg/L Gd^{3+} and gadodiamide Gd from plasma and blood

SAMMS	Matrix	Gd introduction	Percentage removal of 1 mg/L Gd[a]	
			As Gd^{3+} (%)	As gadodiamide Gd (%)
1,2-HOPO	Human plasma	In vitro (spiked Gd)	52	99
	Human blood	In vitro (spiked Gd)	48	99
	Rat blood	In vivo exposure	NA	98[b]
DiPhos	Human plasma	In vitro (spiked Gd)	81	43
	Human blood	In vitro (spiked Gd)	80	61

[a] All measured at liquid per SAMMS ratio of 100 mL/g, 37°C, and 1 hour contact time, reported as average value of triplicate runs, percentage error ~5%.

[b] Blood collected from a chronic renal failure rat 10 days after intravenous injection with 2.5 mmol gadodiamide per kilogram body weight and the blood contained 1.4 mg Gd/L before contact with SAMMS.

increase their size can also be made). Flowing of Gd-contained dialysate and acid through a packed bed column of 1,2-HOPO-SAMMS was performed. Table 2 shows that after seven cycles of sorption of free Gd in dialysate and regeneration with 0.5 M HCl in a packed bed column, the 1,2-HOPO-SAMMS retained its sorption ability. Si dissolution was also monitored at each step as a measure of sorbent stability and was found to be less than 0.1 wt% of the material. The excellent stability of SAMMS is owed to the strong covalent bonding of the organic monolayers and silica substrate as well as high degree of silane cross-linking. The ability to regenerate 1,2-HOPO-SAMMS is potentially beneficial in moving toward personal miniaturized sorbent dialysis systems that use sorbent materials to recycle the dialysate to minimize its volume. In addition, 1,2-HOPO-SAMMS has a long shelf-life; the material has been found to be effective after 7 years under normal ambient conditions. Specifically, the data reported herein were obtained from an exact batch of SAMMS that was synthesized in 2001 and was first publically reported in 2005[16] as a very effective sorbent for lanthanide capture.

SAMMS for removal of free Gd and Gd-chelate from blood

In addition to their feasible use in sorbent dialysis, SAMMS can potentially be used in "hemoperfusion" for direct blood removal of Gd-based contrast agents. Materials that offer fast and rapid removal of Gd-based contrast agents after the Gd-contrast MRI are highly beneficial for a few reasons. First, if the proposed mechanism that transmetallation causes Gd to dissociate from the chelates and triggers NSF is true, the key success in preventing NSF is to remove Gd contrast agents from the blood before they dissociate. Second, rapid removal of Gd-based contrast agents before they leave the intravascular space is advantageous because once they become intracellular, they cannot be effectively removed by either hemodialysis or hemoperfusion. Third, rapid removal of Gd-based contrast agents cuts the treatment time per session and perhaps number of sessions that patients must undergo. Initial evaluation of SAMMS materials for the ability to remove gadodiamide Gd and free Gd (to mimic Gd that is dissociated from Gd-chelates) was performed in batch contact experiments. The percentage removal of 1 mg/L of free Gd and gadodiamide Gd from human blood and plasma using 1,2-HOPO-SAMMS materials is shown in Table 3. At L/S of 100 mL/g, 1,2-HOPO-SAMMS was able to remove 99% of the gadodiamide Gd and about 50% of the free Gd (as spiked to the fluids), suggesting that the material was able to remove the gadodiamide as a whole without dissociating it first. The fact that the free Gd is less effectively removed by the SAMMS than is the gadodiamide Gd suggests that the free Gd is likely to bind with blood components such as proteins. Thus one can conclude that once dissociated from the chelates, free Gd is likely bound with proteins, hence cannot be cleared effectively by conventional dialysis. On the other hand, SAMMS material can be fine-tuned to have a functional group that is powerful enough to compete with proteins for Gd. Table 3 shows that Di-Phos-SAMMS could remove 80% of Gd that was spiked in as-free Gd (but likely bound with proteins in blood). Interestingly, Di-Phos-SAMMS was effective in competing with proteins for the Gd but was not able to capture gadodiamide Gd as effectively (only 40% to 60% removed). One explanation might be simple sterics. It is likely that the HOPO ligands bind with gadodiamide Gd by displacing the amide carbonyls of the gadodiamide, then the rest of the chelating ligand would be filling the remainder of the coordination sphere of the Gd, making strong chelates. The DiPhos ligand is a fairly bulky ligand and might have trouble wedging itself into the two sites previously occupied by amide carbonyls, whereas the HOPO ligand is a planar aromatic and might be able to slip into that vacancy more easily. As a result, HOPO-SAMMS could remove the gadodiamide as a whole, but DiPhos-SAMMS could not. Results in Table 3 also indicate that removal of free Gd (as spiked) and gadodiamide Gd was as effective in blood as in plasma, indicating no competitive binding of the two metal species by red blood cells. Note that for the studies done in human blood and plasma, the two Gd species were spiked into the fluids prior to the batch sorption with SAMMS. Table 3 also shows that 98% of gadodiamide Gd could be removed from the rat blood with in vivo Gd exposure. Specifically, the Gd in rat blood was the result of intravenous injection of 2.5 mmol/ kg body weight gadodiamide to a chronic renal failure rat, and the blood was drawn after 10 days lapse to be used in batch sorption with 1,2-HOPO-SAMMS. This suggests that the HOPO-SAMMS can remove the gadodiamide from blood regardless of how the chelate is introduced to the blood or whether the blood is from human or rat. Lastly, it is worth noting that in large excess of other metals suspected to play roles in transmetallation with Gd in the Gd-chelate (eg, 130 mol Ca, 160 mol Mg, 600 mol Fe, 1.7 mol Cu, and 7 mol Zn per mol Gd), the removal of Gd appeared to not be affected by these competing metals.

After batch evaluation, in moving toward real-world applications, a flow device incorporating HOPO-SAMMS has been constructed and evaluated with heparinized blood. It was designed to have 100-fold scale-down parameters from those of a hemoperfusion system, which normally filters 5 L of blood

(adults) at the blood flow rate of 200 mL/min.[27] Hence, the scale-down system cleans a total of 50 mL whole blood at the flow rate of 2 mL/min. With a particle size of 75 to 200 μm and pore size of 60 Å, heparinized blood could flow freely through the bed of SAMMS, and no blood clotting was observed after 2 hours of hemoperfusion. This is likely owed to suitable particle size and shapes (round), pore size (excluding large molecules), and chemistry of SAMMS (eg, 1,2-HOPO groups are not prone to binding proteins). Besides the specificity to the target toxins, SAMMS has a major advantage over commercial activated carbon in hemoperfusion. The high affinity of activated carbon to blood components such as platelets and its ability to fragment and create emboli formation makes it unsuitable for direct blood contact in a hemoperfusion circuit,[28] whereas SAMMS has proved to be biocompatible for direct blood contact. More data will be reported in due course.

Discussion

To minimize the risk of developing NSF in patients having renal failure, the nanostructure silica material that is functionalized with 1-hydroxy-2-pyridinone ligands has great potential to be used in sorbent dialysis and hemoperfusion systems for the removal of dissociated Gd and chelated Gd (dadodiamide). The 1,2-HOPO-SAMMS material could remove 99% of the dissociated Gd in dialysate in a minute and 95% of dadodiamide in 30 minutes. The material can be easily regenerated. The fast, efficient, and regenerable SAMMS will enable the development of the next-generation personal dialysis systems. With a personal device, dialysis can be performed continuously rather than in three sessions apart per week, which will benefit the clearance of Gd-based contrast agents as delayed hemodialysis results in Gd leaving the intravascular environment and becoming undialyzable. 1,2-HOPO-SAMMS could also remove 99% of gadodiamide directly from blood, thus when used in hemoperfusion will rapidly reduce the Gd level in blood and prevent the Gd from dissociating from the chelate. Once dissociated, Gd can be effectively (80%) removed from blood using Di-Phos-SAMMS. If dissociation of Gd chelate is determined to be significant, mixed sorbent (1,2-HOPO-SAMMS and Di-Phos-SAMMS) may result in the best possible chance at clearance of both dissociated Gd^{3+} and gadodiamide Gd from blood. Likewise, mixed sorbent (eg, 1,2-HOPO-SAMMS and 3,4-HOPO-SAMMS) may give the best possible chance of Gd^{3+} and gadopentetate Gd clearance at varying pH levels of dialysate. Sorbent dialysis and hemoperfusion with SAMMS will provide an effective and predicable strategy for removing the Gd from patients with impaired renal function. This would allow for the continued use of contrast MRI, which is a safe alternative to traditional contrast studies, while removing the risk of NSF.

References

1. Grobner T. Gadolinium: a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic systemic fibrosis? Nephrol Dial Transplant 2006;21:1104-8.
2. Marckmann P, Skov L, Rossen K, Heaf JG, Thomsen HS. Case-control study of gadodiamide-related nephrogenic systemic fibrosis. Nephrol Dial Transplant 2007;22:3174-8.
3. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet 2000;356:1000-1.
4. Galan A, Cowper S, Bucala ER. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy). Curr Opin Rheumatol 2006;18: 614-7.
5. U.S. Food and Drug Administration. FDA requests boxed warning for contrast agents used to improve MRI images. Silver Spring, MD: U.S. FDA; 2007.
6. IMV. 2007 MRI market summary report. Greenbelt, MD: IMV; 2008.
7. Othersen JB, Maize-Jr JC, Woolson RF, Budisavljevic MN. Nephrogenic systemic fibrosis after exposure to gadolinium in patients with renal failure. Nephrol Dial Transplant 2007;22:3179-85.
8. Joffe P, Thomsen HS, Meusel M. Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. Acad Radiol 1998;5:491-502.
9. Okada S, Katagiri K, Kumazaki T, Yokoyama H. Safety of gadolinium contrast agent in hemodialysis patients. Acta Radiol 2001;42:339-41.
10. Tombach B, Bremer C, Reimer P, Matzkies F, Schaefer RM, Ebert W, et al. Using highly concentrated gadobutrol as an MR contrast agent in patients also requiring hemodialysis: safety and dialysability. American J Roent 2002;178:105-9.
11. Penfield JG, Reilly RF. What nephrologists need to know about gadolinium. Nat Clin Pract Nephrol 2007;3:654-68.
12. Prince MR, Zhang HL, Morris M, MacGregor JL, Grossman ME, Silberzweig J, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology 2003;248:807-16.
13. Fryxell GE, Lin Y, Fiskum S, Birnbaum JC, Wu H, Kemner K, et al. Actinide sequestration using self-assembled monolayers on mesoporous supports. Environ Sci Technol 2005;39:1324-31.
14. Fryxell GE, Wu H, Lin Y, Shaw WJ, Birnbaum JC, Linehan JC, et al. Lanthanide selective sorbents: self-assembled monolayers on mesoporous supports (SAMMS). J Chem Mater 2004;14:3356-63.
15. Lin Y, Fiskum SK, Yantasee W, Wu H, Mattigod SV, Vorpagel E, et al. Incorperation of hydroxypyridinone ligands into self-assembled monolayers on mesoporous supports for selective actinide sequestration. Envi Sci Technol 2005;39:1332-7.
16. Yantasee W, Fryxell GE, Lin Y, Wu H, Raymond KN, Xu J. Hydroxypyridinone functionalized self-assembled monolayers on nanoporous silica for sequestering lanthanide cations. J Nanosci Nanotech 2005;5:527-9.
17. Tamagaki K, Yuan Q, Ohkawa H, Imazeki I, Moriguchi Y, Imai N, et al. Severe hyperparathyroidism with bone abnormalities and metastatic calcification in rats with adenine-induced uraemia. Nephrol Dial Transplant 2006;21:651-9.
18. Boyd AS, Zic JA, Abraham JL. Gadolinium deposition in nephrogenic fibrosing dermopathy. J Am Acad Dermatol 2007;56:27-30.
19. High WA, Ayers RA, Chandler J, Zito G, Cowper SE. Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis. J Am Acad Dermatol 2007;56:21-6.
20. Morcos SK. Nephrogenic systemic fibrosis following the administration of extracellular gadolinium based contrast agents: is the stability of the contrast agent molecule an important factor in the pathogenesis of this condition? Br J Radiol 2007;80:73-6.
21. Thomsen HS, Marckmann P, Logager VB. Nephrogenic systemic fibrosis (NSF): a late adverse reaction to some of the gadolinium based contrast agents. Cancer Imaging 2007;7:130-7.
22. Medicines and Healthcare products Regulatory Agency (MHRA). Public assessment report: increased risk of nephrogenic fibrosing dermopathy/ nephrogenic systemic fibrosis and gadolinium-containing MRI contrast agents. MHRA; 2007.
23. Tweed SO, Weaver TR, Cartwright I, Schaefer B. Behavior of rare earth elements in groundwater during flow and mixing in fractured rock

aquifers: an example from the Dandenong Ranges, Southeast Australia. Chem Geol 2006;234:291-307.
24. Gorden AEV, Xu J, Raymond KN, Durbin P. Rational design of sequestering agents for plutonium and other actinides. Chem Rev 2003;103:4207-82.
25. Yantasee W, Lin Y, Fryxell GE, Busche BJ, Birnbaum JC. Removal of heavy metals from aqueous solution using novel nanoengineered sorbents: self-assembled carbamoylphosphonic acids on mesoporous silica. Sep Sci Technol 2003;38:3809-25.
26. Saitoh T, Hayasaka K, Tanaka Y, Kuno T, Nagura Y. Dialyzability of gadodiamide in hemodialysis patients. Radiat Med 2006;24:445-51.
27. Kokot F, Pietrek J, Seredyski M. Influence of hemoperfusion on the concentration of methyldigoxin and hormones in plasma. Kidney Int 1979;15:404-10.
28. Stamatialis DF, Papenburg BJ, Gironés M, Saiful S, Bettahalli SNM, Schmitmeier S, et al. Medical applications of membranes: drug delivery, artificial organs and tissue engineering. J Membrane Sci 2008;308:1-34.