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Review Article

Gadolinium In Medicine-An Evaluation and Update

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Abstract

Gadolinium-Based Contrast Agents (GBCA) are intravenous drugs used in diagnostic imaging procedures to enhance the quality of Magnetic Resonance Imaging (MRI) or Magnetic Resonance Angiography (MRA). FDA alerts concerning potential side effects increased patient and medical concerns. More recent FDA information indicate that ionic gadolinium is released from some GBCAs, potentially causing gadolinium toxicity. We checked if gadolinium is excreted renally without intervention after previous administration of GBCAs, and if chelating agents are effective in removing gadolinium that may have remained in the body after GBCA administration. Through the evaluation of our internal database and the studies of others, we concluded that no clear consensus exists at this time. While the DTPAs may be the choice of chelators for the removal of gadolinium from the human body, further studies are needed to prove this. It seems clear, however, that microcyclic GBCAs provide a lesser risk of causing gadolinium retention and gadolinium toxicity symptoms.

Keywords: Gadolinium, Gadolinium-Based Contrast Agents, GBCA, Chelation, DMPS, DTPA, EDTA, MRI

Introduction

The first contrast agent to incorporate gadolinium was Magnevist® (gadopentetate dimeglumine). This linear GBCA was synthesised in 1981 and approved by the FDA for clinical use in 1988. Since then, a total of 11 GBCAs have been approved by the FDA. Magnevist®, which has been administered globally almost 100 million times, has dominated in clinics for some time (Clough 2019) [1].

According to the FDA, "Gadolinium-Based Contrast Agents (GBCA) are intravenous drugs used in diagnostic imaging procedures to enhance the quality of Magnetic Resonance Imaging (MRI) or Magnetic Resonance Angiography (MRA)". FDA and other agencies relate that the use of GBCAs carries some risk, including allergic reactions (Chen 2011) [2].

While GBCAs were formulated to reduce toxicity risks from unbound gadolinium ions, researchers have pointed out that the paramagnetic properties of ionized gadolinium have facilitated diagnostic advancements, but the use of GBCAs carry some toxicity risk (Do 2020) [3].

On July 27, 2017, the FDA issued a statement concerning data "evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents."

On 05-16-2018, the FDA updated information and stated: "All MRI centers should provide a Medication Guide the first time an outpatient receives a GBCA injection or when the information is substantially changed. In general, hospital inpatients are not required to receive a Medication Guide unless the patient or caregiver requests it. A health care professional who determines that it is not in a patient's best interest to receive a Medication Guide because of significant concerns about its effects may direct that it not be provided to that patient; however, the Medication Guide should be provided to any patient who requests the information." https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201277Orig1s000SumR.pdf

According to information from the European Medicines Agency and the Federal Institute for Drugs and Medical Devices dated Jan. 2018, the long-term risks of gadolinium contrast agent administration remain unknown. As a result, the withdrawal of certain gadolinium-containing contrast agents for Magnetic Resonance Imaging (MRI) was recommended in Germany 2018. The German Federal Institute for Drugs and Medical Devices (Bfarm) [4] extended the suspension for GBCA until Feb. 28, 2022.

In the US, there are currently no restrictions. According to the Drug Safety Communication. Janet Woodcock, M.D. and director of the FDA's Center for Drug Evaluation and Research stated, "The FDA will continue to assess the safety of GBCAs, and to that end, we are requiring GBCA manufacturers to conduct further studies to assess the safety of this class of contrast agents" (FDA 3/16/2018).

Chemical Structure of GBCA

Gadolinium (III) complexes have been utilized as Magnetic Resonance Imaging (MRI) contrast agents for decades. As

Clough and colleagues pointed out concerns have developed about their toxicity, believed to derive from demetallation of the complexes in vivo, including the relatively large quantities of compound required for a successful scan. The stability of GBCAs are thus of high importance, and stability is determined by the ompound's molecular structure.

According to their chemical structure, the Gd-containing contrast agents are subdivided into ionic and nonionic, macrocyclic and linear contrast agents. The cyclic structure creates a strong bond to gadolinium. In contrast, the linear contrast agents are so-called Gd chelates with open, mobile chains that have no strong binding to the toxic Gd3 + ion (Hemsen 2012, Marckmann 2006) [5, 6].

Gadolinium Side Effects and Toxicity

Linear GBCAs are contraindicated for patients with renal impairment. As outlined by Dr. Lucie Yang in the FDA Medical Team Leader's review, there has been great effort to search for the GBCAs distinctive characteristics that can help predict the risk of Nephrogenic Systemic Disease (FDA 2011).

The toxicity of the free Gd^{3+}ion is related to two properties: its insolubility at physiologic pH, resulting in very slow systemic excretion; and an ionic radius close to that of Ca^{2+}that allows Gd^{3+} to compete biologically with Ca^{2+}.

Ramalho et al summarized the literature on GBCAs related to animal and human studies and tied together information on agent stability. In his article, "*Gadolinium-Based Contrast Agent Accumulation and Toxicity: An Update",* he emphasizes that low-stability agents are the ones most often associated with brain deposition of gadolinium as reported in the literature since 2014 (Ramalho 2015) [7].

Ionic gadolinium is a well-known blocker of many types of voltage-gated calcium channels at very low concentrations. It can inhibit physiological processes such as contractions of smooth, skeletal, and cardiac muscles; transmission of nerve impulses; and blood coagulation. Ionic gadolinium also inhibits the activity of certain enzymes, some dehydrogenases and kinases, and glutathione S-transferases, and may increase the expression of some cytokines, inhibit mitochondrial function, and induce oxidative stress.

Spencer et al found that major lesions related to single-dose administration of gadolinium chloride in rats consist of mineral deposition in capillary beds, phagocytosis of minerals by macrophage-like cells, hepatocellular and splenic necrosis followed by dystrophic mineralization, decreased platelet numbers, and increased coagulation times. Other studies determined that gadolinium is a potent inhibitor of the reticuloendothelial system. (Williams 2016)

While ionic gadolinium is considered highly toxic, GBCAs have been listed as nontoxic.

According to FDA information, the GBCA with the linear or chain ligands, especially the non-ionic, are considered most unstable, and carry the highest risk of releasing free Gd, causing gadolinium-related toxicity symptoms and ailments. The stability of the chelation between the gadolinium ion and the ligands is critical for predicting the risk. The macrocyclic GBCAs have a higher stability constant than the linear ones.

Gadolinium Deposition Disease (GDD)

GDD has been proposed as the name for a newly described, not yet widely accepted, condition of gadolinium (Gd) toxicity.

The classic symptoms of the newly postulated but not yet confirmed condition of gadolinium deposition disease (GDD) have been described and include brain fog, head pain, blurred vision and dry eyes, skin burning pain, bone and/or joint pain, neuralgia, and skin discoloration, doughy or thickened skin (Ramalho 2017) [8].

Nephrogenic Systemic Fibrosis (NSF)

In 2006, gadolinium-containing contrast agents were first mentioned as a cause of Nephrogenic Systemic Fibrosis (Agarwal 2009, Grobner 2006) [9 , 10]. Nephrogenic Systemic Fibrosis (NSF) is a potentially fatal disease that causes hardening and thickening of the skin and internal organs. In patients with advanced renal insufficiency, NSF symptoms were seen within days to months after administration of GBCAs. (Nephro-News, issue 1/08) Hobbs and Williams state in their website that "All GBCAs and gadolinium chloride have been found to stimulate fibroblast proliferation in tissues taken from healthy subjects and that may be a major factor responsible for Nephrogenic Systemic Fibrosis (NSF) because proliferation of CD34+ fibroblasts is the hallmark histologic feature of this disease." (Williams 2016)

Among other health effects that have been reported after GBCA administration are nausea, headaches, dizziness, brain fog, pain in skin, bones or joints. The severity of symptoms seems to vary widely (Drugwatch, 2018) [11].

GDD and NSF Observation

Symptoms of NSF may appear longer than one month after administration of GBCAs. In contract, GDD symptoms most often arise within one day, and quite often immediately after injection, suggesting either a toxic or immunological reaction.

In 2019 Semalka and Ramalho observed that many of the individuals afflicted by GDD suffer from an autoimmune disease. The authors relate that their "current thinking is that GDD involves many elements of the immune system, including acute humoral response (granulocytes, mast cells, B cells), subacute response (macrophages, T-cells) and chronic response (circulating fibrocytes)." GDD shows similarity to a combination of acute hypersensitivity reactions and NSF, and this could explain why all GBCAs, regardless of structure, can cause GDD, whereas NSF is primarily associated with less stable linear agents (Semalka 2019) [12].

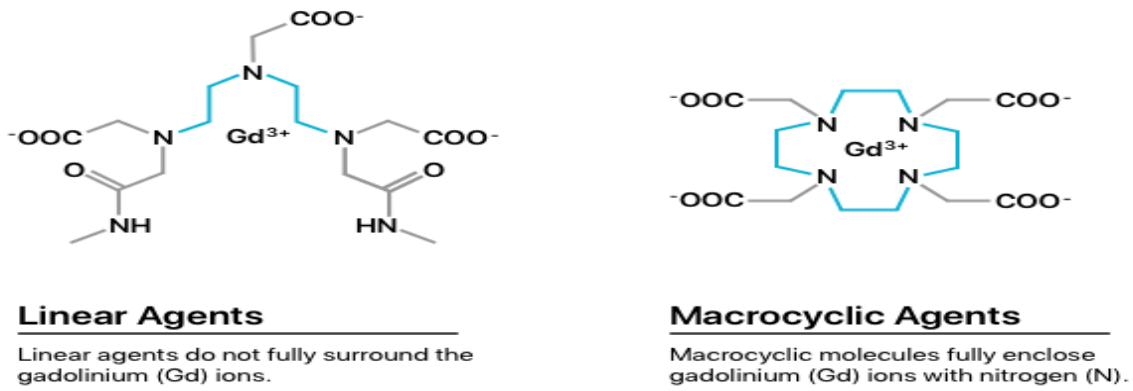

Table 1: Linear vs Macrocyclic Agents

Source: Rogosnitzky, M., Branch S. Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms. Biometals.2016; 29:365-376

To date, several GBCAs are approved by the US Food and Drug Administration (FDA) as shown in Table2. The recommended human dose is 0.1 mmol/kg BW.

Brand name	Generic name	Structure	Gd release %/day
Ablavar	gadofosveset trisodium	Linear i.e.chain, ionic	0.12
Eovist	gadoxetate disodium	Linear i.e.chain, ionic	0.07
Magnevist	gadopentetate dimeglumine	Linear i.e.chain, ionic	0.16
MultiHance	gadobenate dimeglumine	Linear i.e.chain, ionic	0.18
Omniscan	gadodiamide	Linear i.e. chain, non-ionic	0.16
OptiMARK	gadoversetamide	Linear i.e. chain, non-ionic	0.44
ProHance	gadoteridol	Macrocyclic, non-ionic	<0.007
Dotarem	gadoterate meglumine	Macrocyclic, ionic	<0.007
Gadavist	gadobutrol	Macrocyclic, non-ionic	<0.007

Table 2: FDA-Approved GBCAs

Source: FDA Bulletin, FDA Drug Safety Communication, 2011

In 2007, FDA stated that it could identify "no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs." In the years to follow, researchers such as Frenzel and others disproved this statement through animal studies (Jost 2019) [13].

In 2011, the FDA reversed its earlier view and clearly stated that "Linear GBCAs result in more retention for a longer time than macrocyclic GBCAs. Gadolinium levels remaining in the body are higher after administration of Omniscan (gadodiamide) or OptiMARK (gadoversetamide) than after Eovist (gadoxetate disodium), Magnevist (gadopentetate dimeglumine), or MultiHance (gadobenate dimeglumine). Gadolinium levels in the body are lowest after administration of Dotarem (gadoterate meglumine), Gadavist (gadobutrol), and ProHance (gadoteridol)."

Raeschert and colleagues confirmed this and noted in their comparative study that only traces of Dotarem (gadoterate meglumine) were detected in the brain of renally impaired rats, whereas marked Gd retention was observed in almost all brain areas after injections of the L-GBCAs, MultiHance (gadobenate dimeglumine) and Omniscan (gadodiamide) (Raeschert 2018) [14].

FDA documents that the amount of gadolinium released in percent per day is negligible (<0.007%/day) for the macrocyclic, ionic GBCA Dotarem and for the macrocyclic non-ionic GBCAs ProHance and Gadavist (Chen 2011) [2].

In their review, Chehabeddine and colleagues note that all macrocyclic GBCAs continue to be used "as no available valid evidence linked them to brain gadolinium retention. The researchers also state that "there is no evidence to-date that gadolinium retention leads to any disease or disorders in subjects with normal renal function. Further investigations with long-term follow-up are needed" (Chehabeddine 2019) [15].

Gadolinium and Chelation

In medicine, chelation therapy has been used to treat metal poisoning and chronic metal overexposure. It is a chemical process by which a chemical chelating agent is used to bind metal ions, forming metal chelates that are then eliminated by the body. Thus, the use of chelating agents has been introduced to bind gadolinium that has been stored in the human body. An increasing number of physicians consider chelation a promising therapy for patients who have received GBCA.

The molecular structure of each GBCA determines its stability. Magnevist® is a linear molecular complex of DTPA and ionic gadolinium. According to the manufacturer's Material Safety Sheet Magnevist® is a stable compound (Beyer Health Care Pharmaceuticals 2008); however the FDA release of 2011 stated that Magnevist® does release gadolinium at the rate of 0.16%/day. (Table 2)

	Chemical Name	Chemical Formula
GdEDTA	Gadolinium Edetate **	C10H12GdN2O8-
CaEDTA	EDTA Mono Calcium	$C_{10}H_{14}CaN_2O_8$
GdDTPA	Gadopentetat Dimeglumine (Magnevist®*	$C_{28}H_{54}GdN_5O_{20}$
ZnDTPA	Pentetate zinc trisodium	$Na_3ZnC_{14}H_{18}N_3O_{10}$
CaDTPA	Pentetate calcium trisodium	$C_{14}H_{18}CaN_3Na_3O_{10}$

Table 3: Chemical Comparison of GBCA and Chelating Agents

Which type of chelator?

Chelating agents, also called chelators, are chemical compounds that react with metal ions to form a stable, water-soluble complex. Chelating agents compete with body ligands for metals, but due to their specific sulfhydryl, carboxyl or hydroxyl groups their affinity for metals differ.

DMPS (2,3-Bis(sulfanyl)propane-1-sulfonic acid) or DMSA (Dimercaptosuccinic acid*)* contain sulfhydryl groups which bind metals such as arsenic.

The EDTAs (Ethylenediaminetetraacetic acid) bind metals via carboxylate and amine groups and form complexes with Mn(II), Cu(II), Fe(III), Pb (II) and Co(III) by exchanging the existing metal in their particular molecular structure (i.e. Ca in Ca-EDTA).

The DTPAs (Pentetic acid or diethylenetriaminepentaacetic acid) work similarly by complexing agents from the group of synthetic polyaminopolycarboxylic acids which have a high affinity for certain heavy metals and radionuclides.

When CaDTPA (calcium trisodium diethylenetriaminepentaacetate) is used, the calcium ion is exchanged for the corresponding metal ion, provided it has a greater binding constant to DTPA. When ZnDTPA (Zinc diethylenetriaminepentaacetate) is used, the zinc ion is exchanged for the corresponding metal ion, provided it has a greater binding constant to DTPA. Excretion takes place predominantly via the kidneys. (Drisko 2018).

Thus, the EDTAs or DTPAs function by metal exchange. This is not the case for DMSA or DMPS.

Some investigators have looked at the EDTAs and the DTPAs as potential chelators for Gadolinium. Weinmann noted that the stability constant indicates that DTPA binds Gd several magnitudes more tightly than EDTA.(Weinman 1984) [16].

If gadolinium is released from a GBCA as outlined in Table 2, free gadolinium would be available for binding and the EDTAs or DTPAs may potentially decorporate Gadolinium.

Chelating Gadolinium

CaDTPA and ZnDTPA are chelating agents that have been used investigationally for over 40 years, but which of the DTPAs is more suitable for the treatment of gadolinium exposure, has not been evaluated; however for the treatment of internal contamination, FDA recommends to start with the stronger agent CaDTPA and continue with ZnDTPA (FDA 2015) [17].

Semalka et al in their preliminary study of 25 symptomatic patients with Gadolinium Deposition Disease (GDD) report that all patients (18 women; mean age, 46.8 ± 15.3 years) had received at least 1 administration of a gadolinium-based contrast agent. Patients received 3 treatment sessions with Ca-/Zn-DTPA, 15 with treatments spaced 1 month apart, and 10 with treatments spaced 1 week apart. In all cases, every treatment consisted of an application of Ca-DTPA and Zn-DTPA separated by 24 hours. Measurements of 24-hour urine Gd content before dosing and on the first and second days of therapy were performed. Symptomatic improvement of patients was determined by use of a 10-point scale of patient symptoms.

According to Semalka. the gadolinium content increased in the urine with an overall mean of 30.3-fold increase in the monthly regimen ($P < 0.001$) and 12.9-fold in the weekly regimen ($P < 0.001$). Overall, symptoms improved in 13 patients, unchanged in 10, and worsened in 2. Significant clinical improvement was present for headache, brain fog, and bone pain for the monthly regimen and arm pain and leg pain for the weekly regimen (Semalka 2018) [18].

In a follow-up study, published 2019, Semalka and Ramalho listed the basic regimen of the protocol: CaDTPA day 1, ZnDTPA day 2, analog to the protocols used for the "decorporation" of radioactive metals. The process was repeated weekly or monthly, for a total of three chelation treatment time-points. The increase in Gd-excretion was greater following CaDTPA on day 1 than with ZnDTPA on day 2. The researchers noted that even with macrocyclic agents, the urine level of Gd was increased, but by less than half the increase observed for all GBCAs collectively [Semalka 2018] [18].

Prybylski et al in their study on rats could not observe a reduction in Gd concentration in any organ after repeated ZnDTPA treatment. For this study, the animals were injected intravenously with 10 doses of 1 mmol/kg gadodiamide and treated with intravenous Zn-DTPA (30 μmol/kg) concomitantly or 1, 4 or 8 h after GBCA administration (N = 3 rats per group). After euthanization, tissues were harvested three days after the last dose of gadodiamide and tissue Gd

concentrations were assessed by ICP-MS. Additionally, a simulation of a single 0.1 mmol/kg gadopentetate dose with 30 µmol/kg DTPA given either concomitantly or within the first 24 h after GBCA was run; simulated tissue Gd concentrations were compared with those observed in rats to determine if simulated trends were accurate (Prybylski 2019) [19].

Boyken et al. described CaDTPA chelation of Gd in a rodent model with three infusions of Ca-DTPA or saline, once weekly. In their study, they observed that DTPA induced a 10-fold increase of urinary excreted Gd in rodents who had received linear GBCA (e.g. Gadopentetate; Magnevist) but not after a macrocyclic agent (Gadobutrol; Gadavist) (Boyken 2019) [20].

Greenberg reports of a single case report where apparently, chelation therapy removed some retained gadolinium, which could be monitored through 24-hour urine collections. Greenwald summarizes that the risk of gadolinium retention is decreased by using cyclic rather than linear GBCAs. Greenberg reports that in this case "a patient with chronic zinc poisoning from denture cream retained gadolinium after a magnetic resonance imaging procedure, likely due to transmetallation. During chelation therapy, high levels of gadolinium in excreted urine (up to 89 µg/d, 29 days after gadolinium administration) were present, indicating that gadolinium had been retained. Almost 2½ years after gadolinium exposure, a 24-hour urine collection indicated that the gadolinium level remained in the elevated range (0.6 µg/d). This single case report suggests that patients with elevated zinc exposure may be at increased risk of gadolinium retention" (Greenberg 2010) [21].

Greenberg does not mention that gadolinium excretion also happens over time, without intervention.

Gadolinium in Urine Before and After Chelation

To confirm Semalka's results, we evaluated urine received from patients between 2007 to mid-2018. All had received at least one MRI. The exact GBCA i.e. linear or microcyclic, or the time when the GBCA was received was unknown to us.

We compared baseline values with urine samples collected after chelation. We selected sample pairs of patients who had urine collected before and after chelation. For each sample pair, the pre-chelation and post chelation urine was collected on the same day.

We did not find data for gadolinium mono-chelation treatment with CaDTPA or ZnDTPA, but located two sample pairs or pre and post urines involving the combination treatment DMPS+ZnDTPA. This type of chelation protocol was established by Dr. Peter VanderSchaar of Leende, Netherlands. For this combination treatment, DMPS is injected into the vein at 1ml/min and after 10minutes or more ZnDTPA is injected into the same vein. As shown in Table 6, an increase in gadolinium excretion was not noted.

Test value before chelation In mcg/g Creatinine	Urine concentration after Chelation with 1 ampule DMPS plus 1 ampule ZnDTPA	Assessment
696	512	No success
8	5	No success

Table 4: Gd in Urine before and after chelation with DMPS and ZnDTPA

It must be noted that the studies by Semalka involve 24h urine collections. The gadolinium concentration is reported in mcg/24h. The gadolinium test values in Table 4-6 are based on urine creatinine levels. For this, urine creatinine levels are used because this calculation reduces the potentially great margin of error which result from an incorrect sample volume given. In our experience, which is similar to that of other laboratories, the sample volume provided by patient or doctor's assistants is rarely correct and since the mcg/24hr test value is a mathematical conversion involving sample volume, potential errors are not uncommon.

Semalka's research involved the administration of DTPA only, but our database only showed test results for the combination treatment DTPA+DMPS. To rule out errors, we also evaluated baseline urine values with those obtained after chelation with intravenous DMPS. See Table 5

In his product monograph *Dimaval*® published in 2008, Dr. Johann Ruprecht of Heyl, Berlin, manufacturer of DMPS (brand name Dimaval®), lists the physical-chemical parameters of a number of metals. The author outlines pharmacological experiments and publications regarding the bioavailabilty of DMPS and its metal-binding ability. Gadolinium is not listed. According to the author, appropriate publications were not available at this time. Dr Ruprecht had also noted that the question of GBCA safety had not arisen. It was only after 2014 that studies showed that gadolinium is deposited and retained in the brain (Gulani 2017) [22]. Dr. Ruprecht hypothesized that DMPS does not react with gadolinium ions.

For years and for internal research purposes only, Micro Trace Minerals Laboratories had routinely tested gadolinium in urine before and after chelation. We thus evaluated urine data concerning gadolinium from our database to prove or disprove Dr. Ruprecht's hypothesis.

Table 5 shows the gadolinium concentration in urine obtained before and after the intravenous injection of 1 ampule DMPS (250mg). Of the 25 sample pairs, consisting of pre- and post-chelation urine, none showed a higher gadolinium concentration after chelation. We thus confirmed Dr. Ruprecht's statement.

Urine Test Value before Chelation Values in mcg/g Creatinine	Urine concentration after DMPS, 250mg, iv Values in mcg/g Creatinine	Chelation Assessment
3096	2340	No success
563	536	No success
525	507	No success
766	574	No success
3703	2186	No success
238	63	No success
11	10	No success
97	97	No success
91	65	No success
40	35	No success
112	76	No success
230	138	No success
31	32	No success
74	52	No success
21	20	No success
189	178	No success
21	21	No success
109	101	No success
77	60	No success
15	13	No success
494	449	No success
383	318	No success
63	29	No success
11	10	No success
97	97	No success

Table 5: Gadolinium in Urine Before and After Chelation with DMPS

In Germany, a growing number of chelation therapists use the combination treatment DMPS+CaEDTA. The reason behind these combination treatments is the assumption that the contemporaneous administration of two powerful, yet differently acting chelators would be more effective in metal binding and elimination. This novel therapy concept has only recently been established. It involves infusions of DMPS plus CaEDTA, given contemporaneously, one after the other.

In our database, we located only six pairs where baseline urine samples were taken prior to the DMPS/Ca-EDTA mobilization. Table 6 indicates that the gadolinium excretion is higher before chelation takes place.

Urine Test Value before Chelation in mcg/g Creatinine	Urine concentration after DMPS iv, 250mg + CaEDTA, 1,9g iv mcg/g Creatinine	
189	178	No success
1424	1284	No success
46	29	No success
586	281	No success
1865	1788	No success
189	178	No success

Table 6: Gd in Urine Before and After Chelation with DMPS+CaEDTA

Comparing Urine Concentration before and after Chelation

Tables 4 to 6 indicate that the diagnostic assessment of Gd in urine necessitates a comparison with a urine sample taken before and after chelation, or else the gadolinium concentration of the post urine sample leads to misinterpretation of results. If, for example, the chelation therapist bases his treatment schedule on a post urine test value alone, he/she may be under the illusion of a 'chelation treatment success', when in fact the gadolinium excretion in the pre-chelation urine might have been higher than that of the post-chelation sample. The therapist might relate chelation therapy success when in fact the elimination of Gd was due to the body's own excretion ability.

Conclusion

GBCAs remain in the body longer than previously anticipated. We could demonstrate that gadolinium is renally eliminated without the use of chelating agents. Our data also confirms that DMPS does not affect gadolinium binding and excretion. Furthermore and most likely due to a lack of sufficient samples, we were unable to prove that the combined chelation treatment of CaEDTA or ZnDTPA with DMPS promotes gadolinium binding and excretion.

However, data provided by Semalka et al suggests that the DTPAs 'detoxify' gadolinium after GBCA retention or toxicity. Other researchers could not support this. Since FDA demonstrated that gadolinium is released daily from the linear GBCAs, it seems likely that free gadolinium is 'chelated' with the DTPAs and possibly with the EDTAs when each of this type of chelator is administered as a mono-treatment.

We suggest more involved studies that pay close attention to the type of GBCA (linear or macrocyclic) administered prior to chelation as this seems a crucial point in the development and treatment of GDD.

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