

# The use of Ca-/Zn-DTPA for chelation of gadolinium in “Gadolinium Deposition Disease”

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*Gadolinium deposition disease (GDD) has been proposed as the name for a newly described, not yet widely accepted, condition of gadolinium (Gd) toxicity. In this review, we summarize the results from our recently published investigation on the use of Ca-/Zn-DTPA chelation in 25 patients with presumed Gadolinium Deposition Disease (GDD) [1]. We also expand our discussion to include the strengths and weaknesses of our paper, our current thinking on the disease, and more comprehensive possible future treatments for GDD.*

## GDD FEATURES

The classic symptoms of the newly postulated but not yet confirmed condition of gadolinium deposition disease (GDD) have been described as including: brain fog; head pain; blurred vision and dry eyes; skin and skin substrate burning pain; boring bone and/or joint pain; sharp pins and needles pain (neuralgia); and glove and sock changes of skin discoloration, doughy or thickened skin, and pain [2-5]. The typical symptoms that patients experience include those also described in Nephrogenic Systemic Fibrosis (NSF) but are less severe, in particular, as regards changes of the distal arms/hands and distal legs/feet.

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To be classified as suffering from GDD, patients should satisfy several criteria:

- 1). Patients should have undergone an imaging study using a Gd-based contrast agent (GBCA) within one month of symptom onset;
- 2) The symptoms should be new to the patient, i.e. not reflecting any pre-existent disease or symptoms observed prior to GBCA administration;
- 3) There should be evidence of Gd remaining in their system beyond 30 days after administration of gadolinium;
- 4) The patients should have normal or near-normal renal function at the time of the GBCA administration [2 -5].

As with Nephrogenic Systemic Fibrosis (NSF), it is likely that the time range of the disease may be longer than one month after administration of GBCAs, but in the current, early period of defining and establishing the disease, it is prudent that the timeline be conservatively restricted. Unlike NSF, the symptoms of GDD most often arise within one day, and quite often immediately after injection.

## GADOLINIUM DEPOSITION DISEASE (GDD): WHAT'S IN A NAME?

We believe that one advantage of using a name that begins with Gadolinium to describe the condition is that there is no doubt about what the condition refers to. In contrast, for example, Nephrogenic Systemic Fibrosis (NSF), does not really convey a sense of what the disease is about. According to Dorland's Medical Dictionary, a disease is defined as: "... a definite morbid process that has a characteristic train of symptoms...", which applies to GDD. It appears that the persistent presence of Gd could be responsible for the long duration and drawn-out nature of the disease. The term "deposition" suggests a more embedded process than "retention" for example; Gd is embedded in skin and bone. Some observers have suggested the term "associated" but we feel that "associated" does not communicate appropriately the sense of Gd remaining in the body. Thus the term "Gd-associated" may be more applicable to transient symptoms, as described by Carlo Quattrocchi's group [6]. Another alternative term that could be considered for inclusion in a description of the condition is the word "exposure". However this may better describe an acute hypersensitivity reaction, which gives an aspect of transiency and not the concept of Gd remaining in the body.

Some patients have actually wanted to call the condition “poisoning”. However, this usually implies that everyone who receives a similar amount of a causative substance should get similarly sick, which is not the case in GDD.

### EPIDEMIOLOGY

Many of the individuals afflicted by GDD are

- i) women,
- ii) individuals of central to northern European ancestry, and
- iii) suffer from an autoimmune disease.

### HYPOTHETICAL DISEASE MECHANISM

The original hypothesis behind our study of the effect of using a chelating agent to remove Gd in GDD sufferers was that this by itself would be sufficient to cure patients of their symptoms. The chelating agents we used were the calcium and zinc salts of diethylene triamine penta-acetic acid (DTPA) which is approved by the FDA for intravenous administration in the treatment of patients contaminated by heavy metals of the actinide family. Gadolinium is an element of the lanthanide series, which have similar ionic radii and shares a number of chemical characteristics with actinides

Our published results [1], our continued clinical experience and worldwide observations suggest however that chelation alone may not be sufficient to cure many patients.

This has led us to theorize that the disease has two components: 1) the presence of Gd in the body, and 2) the host response to that presence.

Intravenous DTPA may be currently the best available chelating agent; however, if the host response is not addressed, many patients will not recover from the disease.

### HOST RESPONSE

Our 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). Hence it is similar to a combination of acute hypersensitivity

Gd Chelate	Structure Type	Thermodynamic Stability		Kinetic Stability T <sub>1/2</sub> at pH 1.0 at 25° C
		Log K <sub>therm</sub>	Log K <sub>cond</sub> (at pH 7.4)	
Dotarem® (gadoterate meglumine)	Macrocyclic ionic	25.6	19.3	338 hr
Gadavist® (gadobutrol)	Macrocyclic non-ionic	21.8	14.7	43 hr
ProHance® (gadoteridol)	Macrocyclic non-ionic	23.8	17.1	3.9 hr
MultiHance® (gadobenate dimeglumine)	Linear ionic	22.6	18.4	< 5 s
Magnevist® (gadopentetate dimeglumine)	Linear ionic	22.1	17.7	< 5 s
Omniscan™ (gadodiamide)	Linear non-ionic	16.9	14.9	< 5 s
OptiMARK™ (gadoversetamide)	Linear non-ionic	16.6	15.0	< 5 s

**Table 1** Stability constants and structural characteristics of the main Gadolinium-based contrast agents (GBCAs). Currently in Europe, linear GBCAs (apart from a few specific indications) have been withdrawn from the market.

reactions and NSF. The similarity to acute hypersensitivity reaction could explain why all GBCAs, regardless of structure, can cause GDD, whereas NSF is primarily associated with less stable linear agents. Managing the host response is part of our ongoing efforts, not reported in the chelation paper [1].

### CYTOKINES

Our initial analysis of the variability of the response of patients to GBCA injection, which ranges from no response at all, (which we term Gadolinium storage condition, and covers the vast majority of subjects who have received GBCA), to patients suffering from GDD, was stimulated by an article published on a similarly variable response elaborated by *ex vivo* peripheral blood monocyte cells (PBMCs) from different individuals to the presence of *Candida albicans*. The reaction varied also from no response at all to a massive response, as shown by cytokine release [7]. This was also supported by studies performed by the research team of Wermuth and Jimenez [8] who showed a dramatic elevation of various profibrotic cytokines to the presence of all the GBCAs, with differences observed between the agents. Based on all this, our current opinion is that cytokine release may be central to the disease, and thus key to the underlying mechanisms of the disease.

Our rationale behind the therapeutic treatment of GDD individuals relies on the concept that Gd is the precipitating

cause, with Gd deposition reflecting continuous ongoing exposure of Gd, from the continued slow release of Gd (from tissue reservoirs) into the vascular system. Thus if Gd released from GBCAs *in vivo* was the sole causative factor, then simple chelation should suffice. Therefore, our group investigated the off-label use of Ca-/Zn-DTPA for the treatment of symptomatic patients with presumed GDD.

### TREATMENT WITH CA-/ZN-DTPA CHELATION

The best agent currently approved for patient use worldwide is Ca-/Zn-DTPA. In the USA this agent is FDA approved as a “decorporation” agent (similar to a chelator) for a variety of radioactive actinide metals, the best known of which is plutonium. A variety of investigators have looked, somewhat randomly, at a number of chelators, including EDTA and desferrioxamine. What is often missing in these studies is that the fundamental criterion for the appropriateness of a chelator agent, namely that it should have high thermodynamic stability (also known as stability constant) with the element it is to chelate (Gd), and also kinetic stability. Determinations of the thermodynamic and kinetic stability were established for GBCAs at their initial inception. Thus it seems obvious and appropriate to use these same data for assessing rechelating agents that could be used to capture the Gd *in vivo*. Table 1 shows the stability constants and

structural characteristics of the main Gadolinium-based contrast agents (GBCAs). Note that DTPA has a higher stability constant for Gd than other chelating agents and also for other heavy metals. For example, DTPA binds Gd several magnitudes more tightly than EDTA (around 288,000 greater affinity) [9,10].

These data were behind our decision to use Ca-/Zn-DTPA to re-chelate Gd in patients with self-described GDD [1].

The basic regimen of the protocol we used was: Ca-DTPA day 1, Zn-DTPA day 2, in a fashion analogous 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 results of our study showed that Ca-Zn-DTPA increased the urine level of Gd, as measured in 24-hour samples. This increase was substantially higher for linear agents. Also, the increase was greater following Ca-DTPA on day 1 than with Zn-DTPA on day 2. One interesting finding was that even with macrocyclic agents, the urine level of Gd was increased, but by less than half the increase observed for all GBCAs collectively. Overall, there was a mean increase of Gd in urine of 30 fold in monthly regimen and by 12 -fold in the weekly regimen ( $p < 0.001$ ) [1].

Following our experience of intravenous DTPA chelation in humans, Boyken *et al.* [11] described Ca-DTPA 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). In their study they distinguished spontaneous and Ca-DTPA-induced Gd excretion, subtracting the amount of Gd determined in the saline-infusion animals from that in the Ca-DTPA-infused animals and defining the remaining amount as mobilized Gd. The differences between this study and our results [1] could be attributed to differences in the timing of Gd deposition, which could vary from months to years after the latest GBCA exposure [1] and only seven weeks in the rat model [11]. Thus comparison of spontaneous excretion before and after treatment may show different results. In addition, there was no rigorous control of the human study participants, so the possibility can't be excluded that patients might have received previous unrecorded linear GBCA injections. Nevertheless we think that the key factor may reflect characteristics specific to GDD patients, such as the cleavage of the bonds between the macrocyclic agents and Gd; that DTPA is acting as a levering agent of intact chelate out of tissues; or DTPA acting as a carrier molecule of the intact chelate, and of course possibly a combination of all three effects.

### CLINICAL RESPONSE TO CHELATION

In our preliminary study, only mild to moderate improvement of symptoms was observed [1]. Our observation was that three chelation sessions might not be sufficient, and our ongoing current clinical experience and observation of worldwide reports seem to confirm this. Overall there was a mild improvement in most of the patients, with the symptom most consistently improved being brain fog, which is a symptom also described as a prominent feature in lead poisoning [12].

### LABORATORY FINDINGS OF SERUM BIOCHEMISTRY

Three-chelation sessions spaced either one week or one month apart, as carried out in our study, did not give rise to abnormalities in blood chemistry, in particular in the serum levels of cations and metals, including zinc, magnesium and potassium. If sessions are spaced much more closely and at a higher total number, it is not unreasonable to anticipate that perturbations in blood levels of cations or metals may occur. Thus, close surveillance of serum chemistry is indicated if more aggressive chelation is performed.

### FLARE UP REACTION

The flare-up (or flare) reaction is the most common adverse reaction to chelation therapy. In our study, we reported that this occurred in 44% of the patients [1]. We speculate that this reflects a host immune response to the remobilization of Gd in the vascular system, probably primarily through a cytokine response. So, effective re-chelation in a patient with true GDD may result in a flare, and our opinion is that development of flare may be the most specific clinical evidence for the presence of GDD. Flare, as we initially described it, is an intensification of already developed symptoms of GDD. In our more recent clinical experience, we have observed the development of new symptoms of GDD, or expansion of existing symptoms.

### SUMMARY

Our published results using intravenous DTPA to remove Gd from humans, showed that the approach does increase Gd elimination from the body. However, it appears that although patients symptoms improve, they probably require more sessions than we carried out. Also, it seems that the management of the host response might be necessary in order to achieve optimal cure for many patients.

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