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RESEARCH LETTER

Gadolinium is quantifiable within the tissue of patients with nephrogenic systemic fibrosis

To the Editor: Thank you for the expeditious publication of our article, "Gadolinium is detectable within the tissue of patients with nephrogenic systemic fibrosis" (NSF), which reported the discovery of gadolinium (Gd) within tissue of 4 of 7 patients with NSF, formerly nephrogenic fibrosing dermopathy.¹ Although our study provided the first qualitative evidence of Gd within the tissue of patients with NSF, further exploration of the matter is our ultimate goal.

We performed subsequently a quantitative analysis on the 4 tissue blocks used in our first study for which Gd was detected. To do this, multiple 30- μ m sections were cut from tissue blocks and deparaffinized using twice-distilled xylene and ethanol. After drying, the samples were weighed and placed into quartz tubes and digested with trace-metal grade

strong acids to fully oxidize all organic material. Digested samples were then analyzed using inductively coupled plasma mass spectrometry on an instrument (6100 DRC Plus, Perkin-Elmer Life and Analytical Sciences Inc, Wellesley, Mass). Total Gd was monitored at dual masses of 157.924 Da for ¹⁵⁸Gd and 159.927 Da for ¹⁶⁰Gd.

A set of duplicate samples (tissue sections from the same block processed independently) was included to assess precision and reproducibility. Appropriate positive and negative controls were included. Because all tissue in the first pilot study had been obtained from the NSF International Registry (New Haven, Conn), we included an additional sample from the affected skin of a patient with a diagnosis of NSF at the University of Colorado, to ascertain whether results were impacted by tissue processing at any particular laboratory.

Table I. Inductively coupled plasma mass spectrometry quantification of gadolinium in tissue of patients with nephrogenic systemic fibrosis

Sample No.*	Sample weight, mg	Total Gd in solution, ng/mL	Total Gd in sample, $\mu\text{g/g}$ –ppm
2D	2.114	17.083	57.2
2D (duplicate)	1.910	17.033	63.1
4	0.129	0.440	24.1
5A	0.2113	0.144	4.8
7	0.215	3.227	106.2
Original negative control	0.1577	0.000	0
University of Colorado NSF case	1.7080	24.228	100.4
Negative controls [†]			
Laboratory blank 1		0	0
Laboratory blank 2		0	0
Laboratory blank 3		0	0
Laboratory blank 4		0	0
Positive controls [†]			% of standard recovered
Laboratory blank spike 1 (0.2 ng Gd)		0.030	106.1
Laboratory blank spike 2 (1.0 ng Gd)		0.130	92.0
Laboratory blank spike 3 (5.0 ng Gd)		0.652	92.3

Gd, Gadolinium; NSF, nephrogenic systemic fibrosis.

*Refers to sample numbering as detailed in original study.¹

[†]Laboratory blank and laboratory blank spike samples for mass spectrometry controls were prepared in identical quartz tubes and contained either no Gd (laboratory blank) or were spiked with a specified amount of Gd (laboratory blank spike) and were then dissolved to the same volume as the skin samples (7.075 mL).

Using this form of mass spectrometry, the presence of Gd was verified and quantified in all 4 specimens from the prior study, and in the single case of NSF diagnosed at the University of Colorado (Table I). Minimal variance in duplicate samples and appropriate performance of all positive and negative controls was observed.

The data indicate a significant amount of Gd within the skin and soft tissue of patients with NSF, ranging from 5 to 106 ppm. In fact, the average level of Gd in lesional skin was 70 ppm. Using methodology similar to our own, but for unrelated reasons, other investigators had determined already that after a single administration of Gd-based contrast at a standard dose of 0.1 mmol/kg, the elemental metal was retained in the bone of healthy volunteers at an average level of 1.77 ppm for gadodiamide (Gd-DTPA-BMA) and 0.477 ppm for gadoteridol (Gd-HP-DO3A).² It would appear the amount of Gd in the

affected tissue of patients with NSF is approximately 35- to 150-fold higher than the level of retained Gd in the bone of healthy volunteers with normal renal function.

Furthermore, it was interesting that while specimen 5A (an actinic keratosis from the jaw line of a patient with NSF) did contain quantifiable Gd, the amount was significantly less than that of the other 5 specimens taken from skin affected by NSF (specimens 2D, 4, 7, and University of Colorado NSF case). Although variations in sample size and technique hindered a comprehensive analysis, a review of the histopathology suggested a greater overall level of fibrosis and hypercellularity with higher measured levels of Gd within tissue. Admittedly the sample size is small, but the data may suggest not only a role for Gd in inducing fibrosis, but also a dose-dependent response.

Ultimately, it is our hypothesis that in vivo transmetallation (displacement of Gd from the chelating agent) is involved in the mechanism of tissue accumulation. Certain Gd-based contrast agents may be more predisposed than others to in vivo transmetallation, as thermodynamic stability constants and kinetic stability constants (effectively the “strength” with which the Gd is retained by the chelate) vary from one agent to another.³ Iron and/or calcium overload states are also common in renal failure and may heighten the risk of such events. The effect of altered pH and/or competition from other metal ions may explain why some patients with renal failure get NSF, whereas others do not. More problematic to deducing the cause and mechanism will be cases of NSF in which no exposure to Gd is identified.

Until additional information becomes available, we agree with recommendations that urge only cautious and necessary use of Gd-based contrast in patients with a severe impairment of renal function (GFR \leq 15 mL/min).⁴

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CASE LETTER
Death of a dog caused by calcipotriene toxicity

To the Editor: Frankenstein, a 19-pound, 1-year-old pug, often licked his owner's skin, especially after his owner applied calcipotriene ointment to treat chronic plaque psoriasis. One evening when the medication was left unattended, Frankenstein tore open the 30-g tube and ingested approximately 10 g of calcipotriene. After 48 hours, he developed hematemeses and extreme fatigue. His veterinarian contacted the American Society for the Prevention of Cruelty to Animals' poison control center and was given the recommended protocol for calcipotriene poisoning. She also learned that the dog's prognosis was poor, because of the extended period of time since ingestion and the inherent susceptibility of canines to the toxic effects of calcipotriene. Frankenstein's initial blood chemistries revealed hypercalcemia and hyperphosphatemia and elevated blood urea nitrogen, alanine aminotransferase, and secretory aspartyl-protease levels. His urine revealed proteinuria and hematuria. The American Society for the Prevention of Cruelty to Animals' protocol was started within a few hours, but despite the aggressive intervention, the dog passed away within hours.

The ointment contains 0.005% calcipotriene (50 $\mu\text{g/g}$), a synthetic vitamin D₃ analog. Vitamin D₃ analogues may have potent calcemic properties and are potentially more lethal when ingested at smaller doses as compared to parent vitamin D₃ compounds.¹ The introduction of synthetic vitamin D₃ analogs in antipsoriasis petroleum-based ointments has led to numerous reports of toxicity in dogs in the United States and in the United Kingdom.²⁻⁵ Clinical signs of calcipotriene toxicity usually present within 24 to 72 hours of ingestion and include anorexia, vomiting, diarrhea, polyuria, polydipsia, depression, and weakness.⁶ If left uncorrected, hypercalcemia in dogs can lead to primary renal failure and soft

tissue mineralization.⁷ Reports of accidental ingestion of calcipotriene in dogs indicate that 40 to 60 μg calcipotriene per kilogram of body weight can cause severe hypercalcemia and a significant risk of mortality.⁸

While the veterinary literature contains several articles on the topic, we know of only one reference in human dermatologic literature.⁹ Topical calcipotriene is relatively safe in humans, and we are unaware of any reports of toxicity from oral ingestion in humans; however, the low threshold of calcipotriene toxicity in dogs raises concern.¹⁰ Small dogs are at risk even if the contents of a 30-g tube are only partially ingested. Patients are generally unaware of the potential toxicity of ingesting topical medications, which leads to a tendency to handle topical medications less cautiously than oral medications. We encourage specific counseling when prescribing calcipotriene, particularly for pet owners, in order to avoid further tragic pet deaths.

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