

JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY

Register or Login: Password: Auto-Login [Remi

Search This Periodical for

[Advanced Search](#) - [MEDLINE](#) - [My Recent Searches](#) - [My Saved Searches](#) - [Se](#)

JAAD HOME

CURRENT ISSUE

ARTICLES IN PRESS

NEW IN EBLUEPRINTS

PAST ISSUES

SEARCH JAAD

LINK TO OMIM

LINK TO PUBMED

EMAIL NOTIFICATION

ABOUT JAAD

AUTHOR INFORMATION

SUBMIT MANUSCRIPT VIA
EDITORIAL MANAGER

EDITORIAL BOARD

CONTACT JAAD

AAD INFORMATION

PRICING INFORMATION

CME ACCESS

SUBSCRIBE TO JAAD

MY PDA

Volume 56, Issue 4,
Pages 710-712 (April
2007)

◀ [previous](#) 49 of 54 [next](#) ▶

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

[Whitney A. High](#), MD, M Eng^a✉, [Reed A. Ayers](#), PhD^b,
[Shawn E. Cowper](#), MD^c

published online 12 February 2007.

FULL TEXT

FULL-TEXT PDF (84 KB)

CITATION ALERT

CITED BY

RELATED ARTICLES

EXPORT CITATION

EMAIL TO A COLLEAGUE

VIEW GENETIC INFO

Article Outline

- [References](#)
- [Copyright](#)

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.

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

More periodicals:

FIND A PERIODICAL

GO TO PRODUCT CATALOG

samples and appropriate performance of all positive and negative controls was observed.

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, µg/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)		0.030	106.1

Gd)		
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).


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 ($\text{GFR} \leq 15 \text{ mL/min}$).⁴

References

 [return to article outline](#)

1. 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;56:21–26. [Abstract](#) | [Full Text](#) | [Full-Text PDF \(243 KB\)](#) | [CrossRef](#)

2. White GW, Gibby WA, Tweedle MF. Comparison of Gd(DTPA-BMA) (Omniscan) versus Gd(HP-DO3A) (ProHance) relative to gadolinium retention in human bone tissue by inductively coupled plasma mass spectroscopy. *Invest Radiol*. 2006;41:272–278. [MEDLINE](#) | [CrossRef](#)

3. Idee JM, Port M, Raynal I, Schaefer M, Le Greneur S, Corot C. Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. *Fundam Clin Pharmacol*. 2006;20:563–576. [MEDLINE](#) | [CrossRef](#)

4. Center for Drug Evaluation and Research. US Food and Drug Administration World Wide Web site. Public health advisory: public health advisory update on magnetic resonance imaging (MRI) contrast agents containing gadolinium and nephrogenic fibrosing dermopathy (December 22, 2006). Available from: URL:http://www.fda.gov/cder/drug/advisory/gadolinium_agents.htm. Accessed December 30, 2006.

^a Dermatology and Pathology, University of Colorado Health Sciences Center, Denver

^b Materials Science (Biomaterials), Colorado School of Mines, Golden

^c Dermatology and Pathology, Yale University Medical Center, New Haven, Connecticut



Reprint requests: Whitney A. High, MD, M Eng, Dermatology and Pathology, University of Colorado Health Sciences Center, PO Box 6510, Mail Stop F703, Aurora, CO 80045-0510

PII: S0190-9622(07)00207-1

doi:10.1016/j.jaad.2007.01.022

© 2007 American Academy of Dermatology, Inc. Published by Elsevier Inc All rights reserved.

Copyright © 2007 Elsevier, Inc. All rights reserved | [Privacy Policy](#) | [Terms & Conditions](#) | [Feedback](#) | [About Us](#) | [Help](#) | [Contact Us](#) | The content on this site is intended for health professionals.