



Anapol Schwartz

ATTORNEYS AT LAW

INTRODUCTION TO GADOLINIUM LITIGATION

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INTRODUCTION TO NEPHROGENIC SYSTEMIC FIBROSIS

Origins of a Man-made Disease

Nephrogenic Systemic Fibrosis

- First described in 1997 in patients with end stage renal disease (Cowper & LeBoit - unpublished)
- Characterized by scleroderma-like skin changes that mainly affect the limbs and trunk.
- The induration of the skin can progress to cause flexion contracture of joints.

Nephrogenic Systemic Fibrosis

- The fibrotic changes may also affect other organs such as muscles, heart, liver and lungs.
- The disease can be aggressive in some patients leading to serious physical disability or even death.

FIRST PUBLISHED REPORT

Scleromyxoedema-like cutaneous disease in renal dialysis patients.

Cowper et al. The Lancet 16 September 2000

Nephrogenic Fibrosing Dermopathy/Nephrogenic Systemic Fibrosis: Report of a New Case with Literature Review

Daram SR. Amer J Kidn Dis. (Oct. 2005) 46;4:754-759

RESEARCH LETTERS

We thank Karen Brown, Meira Bruce, Colan McCann, David Pemberton, Diane Ritchie, and the Scottish Blood Transfusion Service. The project is funded by the Department of Health.

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- 2 Schman MJ, Jerny A, Culp BC. Use of capillary sodium dodecyl sulfate gel electrophoresis to detect the prion protein extracted from scrapie-infected sheep. *J Chromatogr B Biomed Appl* 1997; 697: 223-29.
- 3 Foster JD, Bruce M, McConnell I, Currie A, Fraser H. Detection of BSE infectivity in brain and spleen of experimentally infected sheep. *Vet Rec* 1996; 138: 546-48.
- 4 Hill AF, Zlotnik M, Ironside J, Collinge J. Diagnosis of new variant Creutzfeldt-Jakob disease by nasal biopsy. *Lancet* 1997; 349: 99-100.
- 5 Goldman W, Hunter N, Smith G, Foster J, Hope J. PrP genotypes and agent effects in scrapie: change in elicit interaction with different isolates of agent in sheep, a natural host of scrapie. *J Gen Virol* 1994; 75: 949-55.

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Scleromyxoedema-like cutaneous diseases in renal-dialysis patients

Shawn E Cowper, Howard S Robin, Steven M Steinberg, Lyndon D Sai, Samardeep Gupta, Philip E LeBoit

15 renal dialysis patients have been identified with a skin condition characterized by thickening and hardening of the skin of the extremities and an increase in dermal fibroblast-like cells associated with collagen remodelling and mucin deposition. The disease closely resembles scleromyxoedema, yet has significant enough clinical and histopathological differences to warrant its designation as a new clinicopathological entity.

Since March, 1997, we have identified 15 renal-dialysis patients in California, Michigan, Ohio, and Mississippi,



Figure 1: A 31-year-old woman with a haemodialysis-associated cutaneous fibrosing disorder.



NEPHROGENIC FIBROSING

Dermopathy/Nephrogenic Systemic Fibrosis: Report of a New Case with Literature Review

- Another case of NFD with systemic fibrosis
 - muscles,
 - diaphragm,
 - pleura,
 - pericardium,
 - great vessels, left ventricle and septum of the heart
- In addition to extensive and subcutaneous involvement.
 - Patient had ESRF
- Original manifestation was tightening of fingers and arms

Daram SR. Amer J Kidn Dis. (Oct. 2005) 46;4:754-759

Gadodiamide-Associated Nephrogenic Systemic Fibrosis: Why Radiologists Should Be Concerned

Skin changes due to NSF

- Slightly raised and erythematous nodular plaque
- Linear and confluent regions of fibrosis.
- Soft-tissue swelling and flexion contractures of hand (with fingers maximally extended).

Broome DR. AJR, Feb. 2007, 188:586-91.

FDA: SERIOUS AND SOMETIMES FATAL NEPHROGENIC SYSTEMIC FIBROSIS/NEPHROGENIC FIBROSING DERMOPATHY

- As of December 21, 2006, FDA had received reports of 90 patients with moderate- to end-stage kidney disease who developed NSF/NFD after they had an MRI or MRA with a gadolinium-based contrast agent.
- A skin biopsy is necessary to make a definitive diagnosis.
- Onset began from 2 days to 18 months
- Worldwide, about 215 patients with NSF/NFD have been reported.
- Of these reports, the medical histories of 75 of these patients were reviewed in detail, and all of the patients had received a gadolinium-based contrast agent for an MRI or MRA.

Epidemiology

- Affects both sexes equally
- Age range reported from 8 to 87 years
- Occurs worldwide in all races

The Footprint of Gadolinium

- Gadolinium occurs naturally in the earth's surface.
- However, it does not appear within the human body naturally, nor is there any means of exposure other than through injection of a gadolinium-based contrast dye.



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

High WA, Cowper SE et al. J Am Acad Dermatol 2007;56:21-6

INTRODUCTION TO THE SCIENCE OF CONTRAST MEDIUMS

Introduction

Non-specific paramagnetic contrast agents (CAs) administered in about 25-30% of all MRIs.

- Approx. 23,000,000 procedures worldwide in 2005
- Approx. 10,000,000 procedures/year in the U.S.
- ACR
- Safety profile classically regarded as being superior to that of the iodinated contrast molecules used in X-Ray-based procedures

IDEAL CONTRAST AGENT

- Should be totally inert,
- Causing no interactions with the organism at any level.
- Should be excreted rapidly and completely.
- All CAs are excreted from the body through glomerular filtration.

Thomsen H. Curr Opin Urol 17:70-76.



GADOLINIUM – A LANTHANIDE ION

- The lanthanide (or lanthanoid) series comprises the 15 elements with atomic numbers 57 through 71
- 'Rare earths'
- Arises from the minerals from which they were isolated
- Not absorbed, breathed, eaten, drunk
- There is NO 'background' rate

Kang HP et al. (2004) Clin Chem 50;4:741-46

Gadolinium

- High paramagnetism
- A form of magnetism which occurs only in the presence of an externally applied magnetic field.
- Physicians tend to be lulled into the false belief that MR contrast media are truly "biologically inert."
- However.....
- Free gadolinium (Gd³⁺) is highly toxic!
- a known heavy metal toxin

Shao-Pow et al. MR Contrast Agents - Physical and Pharmacologic Basics. J MAG RES IMAGING 25:884–899 (2007)

Therefore:

- Gadolinium must be 'chelated'
- The ion must be incorporated into stable, ionically bound complexes with organic chelating agents.
- Chelates improve Gd³⁺ in vivo solubility, tissue distribution, and renal clearance.

Mann – J Comp Assist Tomogr 1993, 17, Suppl I: S19-23

GADOLINIUM CONTRAST AGENTS

- Eliminated via the kidneys
- Biological half life in patients with normal renal function is 1.5 hours.
- In patients with advanced renal impairment elimination half life can be prolonged to 30 h or more.

Idee J-M, et al. Clinical and biological consequences of transmetallation induced by contrast agents for magnetic resonance imaging: a review. *Fund & Clinical Pharmacol*, 2007, 20;6: 563-576.

- The fundamental safety basis for this class of contrast media depends upon the stability of the chelate in vivo.

Runge VM. *Top Mag Reson Imag*, (2001) 12;4:309-314

Questions

- What analysis was conducted of the chelate-gadolinium bond to determine safety after 30 hours in vivo?
 - When were the manufacturers aware of the potential for 'transmetallation'?
- What animal studies were conducted to determine in vivo changes of the Gd³⁺ in the acidic environment and prolonged in vivo exposure?
- What was done by each manufacturer when they became aware of the prolonged half-life time in the renally-impaired?



GADOLINIUM CHELATES

- Chelation eliminates the heavy metal toxicity by preventing the cellular uptake of free Gd³⁺.
- Biodistribution of the molecule stays within the extracellular space and enhancing renal filtration.
- Biological half-life of approx. 1.5 hours (assuming normal renal function).

Runge VM. Top Mag Reson Imag, (2001) 12;4:309-314

“It seems reasonable, however, to suggest caution in the use of any of these agents in patients with seriously impaired renal function in which circumstances the material is retained for a prolonged period.”

Dawson P, Gadolinium Chelate MR Contrast Agents (Editorial) Clin Radiol (1994) 49:439-442.

- The fundamental safety basis: stability of the chelate in vivo.
- Hold the metal ion very tightly
- Assures near 100% excretion,
- Chelates made possible the clinical use of gadolinium as an IV CA.

Runge VM. Top Mag Reson Imag, (2001) 12;4:309-314

- An essential feature which influences the binding between the Gd³⁺ and the chelate is the configuration of the molecule
- Two categories of gadolinium chelates
- Macrocyclic molecules (‘ringed’) where Gd³⁺ is caged in pre-organized cavity of the ligand.
- Linear molecules
- The cyclic molecule offers a better protection and binding to Gd³⁺ in comparison to the linear structure.

Runge VM. Top Mag Reson Imag, (2001) 12;4:309-314

TRANSMETALLATION

- A general chemical reaction type describing the exchange of ligands between two metal centers.
- Endogenous metal ions (zinc, copper, calcium, and iron) may compete with Gd³⁺ for binding sites on the ligand.
- These cations can, in theory, displace Gd³⁺ at physiologic pH.
- Likely to occur when the Gd-chelate remains in the body for a long period
- ESRD including those on dialysis.

Mann – J Comp Assist Tomogr 1993, 17, Suppl I: S19-23

- Free gadolinium is highly toxic
- Animal studies
- splenic degeneration,
- central lobular necrosis of the liver

- variety of hematological abnormalities.
- The power of intracellular Gd to cause injury is well known and exploited in some fundamental biological studies.
- The result of this type of injury, classically, is inflammation and fibrosis.

Peter Dawson (personal communication) – April, 2007

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- Therefore, it is crucially important that Gd³⁺ should be strongly attached to a chelate to avoid its toxic effects.
- Transmetallation is dependent on the molecular conditional thermodynamic stability.

Broome DR. AJR Feb. 2007, 188:586-591

- There is evidence that transmetallation can be found in vivo.

PHYSICOCHEMICAL CHARACTERISTICS OF COMMERCIALLY AVAILABLE GADOLINIUM-BASED MR CONTRAST AGENTS

- For stability in vivo, a high thermodynamic stability is desired
- A low dissociation rate is also desirable
- Overall stability in vivo is determined by the interplay between these 2 characteristics.

Khurana – Invest Radiol (2007) 42:139-145)

GADOLINIUM

Case Selection and Rejection Criteria

How is the diagnosis made? Animal studies

Definitive diagnosis of NFD/NSF is made by full-thickness skin biopsy at the involved site.

Weiss et al., Nature Clinical Practice Nephrology (2007) 3, 111-115

Characteristic histological findings include thickened reticular dermal collagen bundles with dermal spindle cells that stain positive for both CD34 and procollagen. These spindle cells are thought to have the immunophenotype of circulating fibrocytes, which are characterized as circulating cells of bone marrow origin that express markers of both connective tissue cells and circulating leukocytes. Extensive mucin deposition is often seen between collagen bundles, but in contrast to other fibrosing disease states, inflammatory cells are usually absent.

Punch biopsy tools

These come in a variety of sizes. Family practice physicians use them routinely, but some do not go deeper than 5 mm and refer to dermatologist for deeper penetration.

Histopathologic Features

Specimen shows markedly increase cellularity with spindle-shaped fibrocytes and mucin with thickened collagen bundles that infiltrate deeply, extending into and widening the septa of the subcutaneous fat.

WHAT CASES TO TAKE?

If NSF/NFD is confirmed by biopsy, take the case.

If NSF/NFD is not confirmed by biopsy, do not take the case, until and unless it is confirmed.

- Traditional approach of getting medical records and having an expert review them will not work.
- Clients need to be told up front that there is no provable case without positive biopsy.
- Find a friendly dermatologist who will do punch biopsies.



GADOLINIUM-BASED MAGNETIC RESONANCE CONTRAST AGENTS: THE MANUFACTURERS AND THEIR PRODUCTS

“Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs. These reports have not always identified a specific agent. Where a specific agent was identified, the most commonly reported agent was Omniscan, followed by Magnevist and OptiMARK. NSF has also developed following the sequential administration of Omniscan and MultiHance and Omniscan and ProHance”

FDA Updated Alert, May 23, 2007

“Five GBCAs (Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance) are approved in the U.S. for magnetic resonance imaging (MRI)... NSF has been reported following administration of all five FDA approved gadolinium-based contrast agents (Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance).”

FDA Updated Alert, May 23, 2007

“The development of NSF in patients with renal disease has followed the administration of some, but not all, of the FDA-approved GBMCAs. To date, the development of NSF has been associated with the isolated prior administration of—especially and clearly predominantly—Omniscan (at rates that exceed those associated with simple market share), but also Magnevist and Optimark.”

ACR Guidance Document for Safe MR Practices: 2007

Table 1: Currently marketed gadolinium contrast agents

Brand name	Generic name	Acronym	Chemical structure	Charge	Cases of NSF
Omniscan	gadodiamide	Gd-DTPA-BMA	Linear	Non-ionic	Yes
OptiMARK*	gadoversetamide	Gd-DTPA-BMEA	Linear	Non-ionic	Yes
Magnevist	gadopentetate dimeglumine	Gd-DTPA	Linear	Ionic	Yes
MultiHance	gadobenate dimeglumine	Gd-BOPTA	Linear	Ionic	No
Primovist	gadoteric acid disodium salt	Gd-EOB-DTPA	Linear	Ionic	No
Vasovist	gadofosveset trisodium	Gd-DTPA	Linear	Ionic	No
ProHance	gadoteridol	Gd-HP-DO3A	Cyclic	Non-ionic	No
Gadovist	gadobutrol	Gd-BT-DO3A	Cyclic	Non-ionic	No
Dotarem	gadoterate meglumine	Gd-DOTA	Cyclic	Ionic	No

*OptiMARK is not licensed in Europe, but is available in the USA

OMNISCAN: DEVELOPMENT AND CORPORATE HISTORY

- Developed by Salutar in California
- Right transferred to Sterling Winthrop (Kodak Subsidiary)
- Imaging division sold in 1994 to Nycomed AS (Norway)
- Amersham plc acquires rights to Omniscan in 1997
- General Electric purchases Amersham plc in 2004
- GE Medical Systems become GE Healthcare
- GE creates additional subsidiary, GE Healthcare Biosciences Corp. as successor to Amersham plc

Omniscan Defendants

- GE
- GE Healthcare
- Amersham Biosciences (part of GE Healthcare)

Omniscan Gadodiamide Injection

- Chemical name is Gadodiamide
- Acronym is Gd-DTPA-BMA
- Is a linear, non-ionic formulation
- Indicated for IV use in MRI to visualize lesions with abnormal vascularity in the brain, spine, and associated tissues
- FDA approval of NDA #020123 on 1/8/93





OVERVIEW OF OMNISCAN PACKAGE INSERT (OCTOBER 2005)

Special populations:

“...studies have not been systematically conducted to determine the optimal dose and optimal imaging time in patients with abnormal renal function or renal failure, in the elderly, or in pediatric patients with immature renal function.”

Adverse Reactions

“Skin and appendage disorders: Pruritis [itching], rash, erythematous rash, skin discoloration, sweating increased, urticaria [hives].”

Contraindications: “None known.”

Warnings: “Increased hemolysis [destruction of RBCs] in the presence of anemia; patients with history of allergy or drug reaction should be observed for several hours after drug administrations.”

PRECAUTIONS:

“...OMNISCAN is cleared from the body by glomerular filtration...Dose adjustment in renal or hepatic impairment have not been studied. Caution should be exercised in patients with impaired renal insufficiency with or houthepatic impairment.”

OPTIMARK: DEVELOPMENT AND CORPORATE HISTORY

- Developed by Mallinckrodt, Inc. (St. Louis)
- In 2001, Mallinckrodt was purchased by Tyco International (US) and was made a part of Tyco Healthcare Group LP
- As of July 2, 2007, Tyco Healthcare will become Covidien Ltd. Mallinckrodt, Inc. will remain a subsidiary of Covidien

OptiMARK Defendants

Tyco Healthcare
Mallinckrodt Pharmaceuticals, Addiction Treatment / A Collaborative Effort
Covidien

OptiMARK Drug Overview

- Chemical name is gadoversetamide
- Acronym is Gd-DTPA-BMEA
- Is a linear, non-ionic formulation
- Indicated for use with MRI in patients with abnormal blood brain barrier or abnormal vascularity of the brain, spine and associated tissues
- FDA approval of NDA nos. 20-937, 20-975 and 20-976 on December 8, 1999



OVERVIEW OF OPTIMARK PACKAGE INSERT (AUGUST 2006)

Special Populations:

“...Renal impairment was shown to delay the elimination of gadoversetamide...”

Adverse Reactions: Skin and Appendages:

“...erythema multiforma [dark red macular eruptions], pruritis, rash macular-papular and vesiculous bullous, urticaria...”

Warnings:

“...increased hemolysis in presence of anemia, patients with history of allergy, renal insufficiency or drug reaction should be observed for several hours after drug administration. (See PRECAUTIONS.)”

PRECAUTIONS:

“Since gadoversetamide is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function. Dose adjustments in renal impairment have not been studied. Dialysis may be needed to clear OptiMARK Injection if it is administered in patients with significant renal impairment. OptiMARK injection has been shown to be removed from the body by hemodialysis...”



MAGNEVIST: DEVELOPMENT AND CORPORATE HISTORY

- Developed by Schering AG in Germany
- Schering establishes New Jersey-based Berlex, Laboratories, Inc. in 1979
- In July 2006, Germany-based Bayer AG completes its acquisition of Schering AG
- Resulting US-based entity is Bayer Healthcare Pharmaceuticals, Inc. in Wayne, New Jersey

The “Magnevist” Defendants

Bayer HealthCare
Berlex
Bayer

Magnevist

- Chemical name is Gadopentetate Diglumine
- Acronym is Gd-DTPA
- Indicated for use with MRI in adults and pediatric patients to visualize lesions with abnormal vascularity in the brain, spine and associated tissues. Magnevist Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.
- Berlex obtained FDA Approval of NDA 019596 on June 2, 1988. This was the first Gd-based contrast agent approved for use in the US.

OVERVIEW OF MAGNEVIST PACKAGE INSERT (USA, NOVEMBER 2002)

Adverse Reactions:

(Skin): Rash, sweating, pruritis, urticaria (hives), facial edema, erythema multiforme, epidermal necrolysis [death and dissolution of tissue], pustules.

Contraindications: None

Warnings:

“...Patients with a history of allergy, drug reactions, or other hypersensitivity-like disorders should be closely observed during the procedure and for several hours after drug administration.”

General Precautions:

“since [Magnevist] is cleared from the body by glomerular filtration, caution should be exercised in patients with impaired renal function. In such patients, increases in serum creatinine and acute renal failure have been reported rarely. Magnevist is not significantly eliminated by the hepatobiliary enteric pathway, but is dialyzable. Caution should be exercised in patients with either renal or hepatic impairment.”

Overview of Magnevist Package Insert (USA, February 2007)

Acute renal failure:

“In patients with renal insufficiency, acute renal failure requiring dialysis or worsening of renal function have occurred, mostly within 48 hours of Magnevist Injection. The risk of these events is higher with increasing dose of contrast. Use the lowest possible dose and evaluate renal function in patients with renal insufficiency.”

Overview of Magnevist Package Insert (S. Africa, 11/15/02)

Special precautions:

“In impaired renal function, the benefits must be weighed particularly carefully against the risks before deciding to perform the examination. Because heterotopic secretion takes place only slowly in the presence of impaired renal function, the retention time in the organism is prolonged in such cases...In severely impaired renal function or chronic renal failure, elimination of gadopentetate can be effected by means of extracorporeal hemodialysis.”

PROHANCE/MULTIHANCE: DEVELOPMENT AND CORPORATE HISTORY

- Prohance was developed by Bracco International B.V. and US-based Squibb. Multihance was developed by Bracco Diagnostic in collaboration with its Italian affiliate Bracco Chimica S.p.A.
- In 1994 Bracco formally acquired the diagnostics division of Squibb and established Bracco Diagnostics Inc. and Bracco Research USA in Princeton, New Jersey
- Both Prohance and Multihance are manufactured for Bracco Diagnostics Inc. by ALTANA Pharma AG in Singen, Germany. ALTANA is now part of the Nycomed Group (as of 1/1/07). Bracco ALTANA Pharma is a joint venture between Bracco S.p.A and ALTANA Pharma AG regarding central European pharmaceuticals.

Potential Prohance/Multihance Defendants

Bracco Diagnostics
Bracco - Life from Inside
Bracco Research USA inc.

ProHance

- Chemical name is Gadoteridol
- Acronym is Gd-HP-DO3A
- Is a cyclic (also called macrocyclic) non-ionic formulation
- Indicated for use in MRI in adults and children (>2 yrs) to visualize lesions with abnormal vascularity in the brain, spine, and associated tissues, and to visualize lesions in the head and neck for adults
- FDA approval of NDA #020131 on 11/16/92



PROHANCE PACKAGE INSERT OVERVIEW (JULY 2002)

Precautions:

“Gadoteridol is cleared from the body by glomerular filtration. The hepato-biliary enteric pathway of excretion has not been demonstrated with Prohance. Dose adjustments in renal or hepatic impairment have not been studied. Therefore caution should be exercised in patients with either renal or hepatic impairment.”

- No specific warning regarding nephrotoxicity
- Dermal side effects: Pruritis, rash, macular papular, urticaria, hives
- Contraindications: None known.





MULTIHANCE GADOBENATE DIMEGIUMINE

- Chemical name is gadobenate diglumine
- Acronym is Gd-BOPTA
- Is a linear ionic formulation
- Indicated for use with MRI of the CNS in adults to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues
- FDA approval of NDA #0201357 and #0201358 on November 23, 2004

Multihance Package Insert Overview (November 2004)

Renal Impairment:

“...the overall extent of elimination of gadobenate was not influenced by impaired renal function. Also, no differences were noted in renally impaired patients in the rate and type of adverse events reported compared with healthy volunteers, and no deterioration in renal function was observed in this population following the administration of Multihance. Therefore, dosage adjustment is not recommended.”

Contraindications:

“...patients with known allergic or hypersensitivity reactions to gadolinium or any other ingredients, including benzyl alcohol.”

Adverse reactions: (Skin and appendages)

“Pruritis, sweating, urticaria”