Risk Factors for Developing Gadolinium-Induced Nephrogenic Systemic Fibrosis

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REQUEST

Nephrogenic systemic fibrosis (NSF) has been reported in patients with renal insufficiency exposed to gadolinium-containing contrast agents. Are there any medications or factors other than renal dysfunction that may increase the risk of developing NSF in individuals who receive contrast agents containing gadolinium?

RESPONSE

BACKGROUND

NSF, formerly known as nephrogenic fibrosing dermopathy, was first described in 1997 in renal transplant recipients. Since 1997, more than 215 cases have been reported.[1] NSF is a fibrosing disorder that predominantly involves the skin but can also affect the liver, heart, lungs, diaphragm, and skeletal muscle. NSF can lead to severe physical disability and death. Although the exact cause of NSF has not yet been proven, significant underlying renal dysfunction has been present in all documented cases, and virtually all patients who have developed NSF were exposed to gadolinium, a magnetic resonance imaging (MRI) contrast agent, prior to the onset of NSF symptoms.[2]

Author information provided at the end of the text.

OBJECTIVE: To identify medications and other potential risk factors, in addition to renal dysfunction, for developing gadolinium-induced nephrogenic systemic fibrosis (NSF).

DATA SOURCES: Information was obtained from PubMed, *International Pharmaceutical Abstracts*, Iowa Drug Information Service, and Google Scholar, using the unlimited search terms nephrogenic systemic fibrosis, NSF, nephrogenic fibrosing dermopathy, NFD, gadolinium, gadodiamide, gadoversetamide, gadopentetate, gadobenate, and gadoteridol. Information was also obtained from the Food and Drug Administration, as well as the manufacturers of the above-mentioned products. Data were collected during April and May 2007.

STUDY SELECTION AND DATA EXTRACTION: All identified articles and information were evaluated. Articles and other information that included data regarding concurrent medications, disease states, and other risk factors for developing gadolinium-induced NSF were included in this review, as were clinical practice guidelines.

DATA SYNTHESIS: NSF is a mysterious and severe disorder that occurs in individuals with severe renal impairment. Virtually all cases of NSF have been associated with the administration of gadolinium-containing contrast media. However, not all renally impaired patients who receive gadolinium develop NSF. Thus, additional risk factors for the development of NSF have been suggested. These risk factors include medications that could cause transmetallation of gadolinium, medications that could cause acidosis, and high doses of erythropoietin. Concomitant medical conditions, including hyperphosphatemia, acidosis, recent surgery, hepatic disease, hypercoagulability, and proinflammatory processes may also predispose patients to NSF.

CONCLUSIONS: Gadolinium-based contrast agents should be avoided in patients with significant renal impairment unless the benefits clearly outweigh the risks. If gadolinium is required, nonionic linear chelates (eg, gadodiamide, gadoversetamide) should not be used. Renally impaired individuals who require gadolinium should be screened proactively for underlying disease states and concomitant drugs that may increase their risk of developing NSF; therapy should be adjusted accordingly.

KEY WORDS: contrast media, erythropoietin, gadolinium, nephrogenic systemic fibrosis.

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GADOLINIUM AND THE CHARACTERISTICS OF FDA-APPROVED AGENTS

Five gadolinium-based contrast agents are approved by the Food and Drug Administration (FDA) for use during MRI: gadodiamide, gadoversetamide, gadopentetate dimeglumine, gadobenate dimeglumine, and gadoteridol. To date, NSF has been reported with all gadolinium-containing products, with the exception of gadoteridol.[2] Currently, there are no FDA-approved contrast agents for magnetic resonance angiography (MRA), although the gadolinium-based products are commonly used for this purpose. The doses of contrast used for MRA may be up to 3 times higher than those approved for MRI. The amount of contrast agent (as a single dose or as a cumulative dose) may increase the risk for developing NSF.

In healthy individuals, gadolinium-containing products are rapidly cleared from the body, with an elimination half-life of approximately 2 hours.[3] However, in patients with renal dysfunction, the elimination half-life is significantly prolonged, reportedly from 30 to 120 hours. Although gadolinium products are cleared by hemodialysis, with one report suggesting 78% elimination with the first hemodialysis session, 96% with the second, and 99% with the third,[2] it has been demonstrated that the effective clearing of gadolinium varies with different hemodialysis membranes.[2] Peritoneal dialysis does not effectively clear gadolinium. A half-life of more than 52 hours has been reported in patients undergoing peritoneal dialysis.[2]

Free gadolinium is toxic to tissues and unsafe for human use.[1] To prevent toxicity, gadolinium is sequestered by binding it to a chelate to form a stable gadolinium-ligand complex. It is hypothesized that the adverse effects associated with gadolinium may be the result of dissociation of the gadolinium-ligand complex in vivo.[3,4] Free gadolinium may then combine with phosphate, carbonate, or other ions and precipitate in skin, muscle, bone, and various organs, leading to tissue injury and inflammatory responses.[3]

Gadolinium-containing contrast agents are classified on the basis of chelate biochemical structures (macrocyclic vs linear) and chelate charge (ionic vs nonionic).[1] Macrocyclic molecules bind gadolinium more tightly than do linear chelates, are more stable, and have lower dissociation rates. Ionic cyclic chelates are thought to be the least likely to release free gadolinium, whereas nonionic linear chelates are the most likely to release free gadolinium in the body.[5] Gadodiamide, the agent most commonly associated with NSF thus far, is a nonionic contrast agent that uses a linear chelate.[1,5] Gadoteridol, the only FDA-approved gadolinium-based contrast agent to use cyclic chelate, has not yet had reports of NSF associated with its use. The characteristics of the 5 FDA-approved gadolinium-based contrast agents are provided in Table 1.[5]

CONCURRENT DRUGS THAT MAY INCREASE THE LIKELIHOOD OF DEVELOPING NSF

Both endogenous metals and acids may destabilize the gadolinium-ligand complex, resulting in dissociation of gadolinium.[3,4] Di- or trivalent metals (eg, iron, zinc, copper, calcium), as well as agents such as lanthanum, may compete with gadolinium and displace it from the complex via transmetallation.[2-4] Transmetallation has been reported to occur more easily with gadodiamide than with other gadolinium-containing agents.[5] Hyperphosphatemia may also be problematic; phosphate may compete for the chelate molecule, causing dissociation of gadolinium.[2] In many published reports of NSF, concurrent medications were not identified. However, in several cases, patients with NSF were currently receiving iron, calcium, and/or lanthanum products.[4,6-8]

The gadolinium-ligand complex may be less stable in acidic environments. Grobner[3] observed 9 patients with end-stage renal disease who received gadolinium-based contrast dye during MRA. Five of the patients developed NSF. At the time of MRA, all of the affected patients had some degree of metabolic acidosis and significantly decreased bicarbonate levels; conversely, the 4 nonaffected patients had normal pH and bicarbonate levels. Grobner suggested that metabolic acidosis should be corrected prior to administration of gadolinium-based contrast agents in patients with end-stage renal disease.

Khurana et al.[9] reported 6 cases of NSF associated with gadolinium-based contrast agents. In those patients, serum bicarbonate levels were normal; however, 5 of the 6 patients had an increased anion gap. On the other hand, there are several documented cases of NSF in individuals with normal or near-normal bicarbonate levels.[10,11]

Table 1. Gadolinium-Based Contrast Agents Currently Marketed in the US[5]

Brand Name	Generic Name	Chemical Structure	Charge	Reported Cases of NSF
Omniscan	gadodiamide	linear	nonionic	yes
OptiMARK	gadoversetamide	linear	nonionic	yes
Magnevist	gadopentetate dimeglumine	linear	ionic	yes
MultiHance	gadobenate dimeglumine	linear	ionic	yes
ProHance	gadoteridol	cyclic	nonionic	no

NSF = nephrogenic systemic fibrosis.

Medications that can cause or aggravate acidosis may contribute to the development of NSF. Sevelamer, although not significantly absorbed systemically, has been noted to aggravate metabolic acidosis, possibly by releasing hydrochloric acid in the gut.[12] Concurrent sevelamer use has been documented in multiple cases of NSF.[4,12-14] Metformin, nucleoside analogs (eg, lamivudine, telbivudine), and other drugs that may cause lactic acidosis could, theoretically, contribute to the development of NSF in individuals with significant renal dysfunction.

A study by Swaminathan et al.[15] suggested that high doses of erythropoietin may be involved in the development of NSF. They evaluated 72 patients (22 with NSF, 50 controls) with end-stage renal disease who were receiving erythropoietin. Patients who developed NSF received a significantly higher dose of erythropoietin than did control patients (average 427 units/kg/wk vs 198 units/kg/wk). The investigators suggested that the association between high-dose erythropoietin and NSF may indicate a link between erythropoietin resistance and NSF (eg, a prolonged inflammatory state). They also acknowledged that high doses of erythropoietin may be an independent contributor to NSF. In many documented cases of NSF, patients were also receiving erythropoietin.[4,5,6,8,12,15] However, it should be noted that most patients with significant renal disease receive erythropoietin.

ADDITIONAL NONPHARMACOLOGIC RISK FACTORS

In addition to the items mentioned above, other proposed risk factors for the development of NSF include hypercoagulable states/thrombotic events, recent surgery, chronic hepatic disease or hepatorenal syndrome, idiopathic pulmonary fibrosis, proinflammatory processes, and significant infection.[2,11,16,17]

GUIDELINES FOR GADOLINIUM ADMINISTRATION

Recommendations regarding the avoidance of gadolinium-based contrast agents vary. The FDA recommends using alternate (non-gadolinium) imaging methods whenever possible in individuals with moderate-to-severe renal dysfunction, which is defined as glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2. The FDA further recommends that if these patients must receive gadolinium-based contrast, prompt hemodialysis should be considered.[18] The European Community Pharmacovigilance Working Party indicates that gadodiamide is "strictly contraindicated" in patients with renal failure and should not be used in patients with severe renal impairment (GFR <30 mL/min/1.73 m^2) or those who have undergone or are undergoing liver transplantation.[5] They also warn physicians to be cautious about using gadolinium-based contrast agents in children younger than 1 year of age due to immature kidney function.[5] The 2007 American College of Radiology Guidance Document for Safe Magnetic Resonance Practices indicates that patients with any level of renal dysfunction should not receive the specific product gadodiamide for magnetic resonance examinations.[2] It recommends avoiding all gadolinium-based contrast agents in individuals with stage 3, 4, or 5 kidney disease (GFR <60 mL/min/1.73 m^2) or those with acute kidney injury unless a risk–benefit assessment indicates that the benefit of receiving such contrast clearly outweighs the potential risks. When benefit clearly outweighs risk, the guidelines recommend obtaining informed consent and using the lowest possible diagnostic dose, such as 50% of the standard dose. Patients on hemodialysis should be transported to hemodialysis immediately following the examination. Hemodialysis should be initiated within 2 hours of gadolinium administration and a repeat dialysis session should be considered within 24 hours. These guidelines also indicate that increased levels of phosphate, iron, zinc, copper, and lanthanum may increase the potential for development of NSF. They also acknowledge that acidosis, inflammatory, and/or thrombotic process may increase the risk of developing NSF; however, these risks have not been "reproducibly established."

Discussion

Several products, including iron, zinc, copper, calcium, lanthanum, sevelamer, and high doses of erythropoietin, have been associated with the occurrence of NSF when used concurrently with gadolinium. Other factors, including hyperphosphatemia, acidosis, recent surgery, hypercoagulability, proinflammatory processes, and hepatic disease, may also increase the risk of NSF. We recommend avoiding the use of gadolinium-containing products whenever possible in patients with renal insufficiency (GFR <60 mL/min/1.73 m^2), especially those with any of the concomitant risk factors or concurrent medications mentioned above. If gadolinium administration is absolutely necessary, nonionic linear products such as gadodiamide and gadoversetamide should not be used. A cyclic molecule such as gadoteridol would likely be a safer alternative.

Additionally, practitioners should consider temporarily holding medications that could be involved in transmetallation of gadolinium. In most instances, temporarily holding products that contain di- or trivalent metals (eg, multivitamins, aluminum, iron, zinc, copper, calcium) would not cause harm and may decrease the risk for transmetallation of gadolinium, thus potentially decreasing the risk of NSF. Clinicians should consider stopping these medications prior to the administration of gadolinium and holding them until reasonably certain that gadolinium has been cleared from the body.

Hyperphosphatemia, in and of itself, appears to be associated with an increased risk for developing NSF. Thus, the

decision to hold lanthanum, sevelamer, or potential aluminium- or calcium-containing agents used for controlling hyperphosphatemia is complex. It is unknown which poses a greater risk—hyperphosphatemia or the agents used to treat it. Therefore, it is difficult to make specific recommendations regarding the continuation or discontinuation of lanthanum or sevelamer, especially in individuals with hyperphosphatemia, despite therapy. Using a non–gadolinium-containing agent in this population would be prudent.

The gadolinium complex may be less stable in acidic environments, and some suggest correcting acid–base disturbances prior to gadolinium administration. This approach appears to be reasonable. Clinicians should be very cautious when administering gadolinium to patients concurrently taking acidosis-associated medications such as metformin and nucleoside analogs. Metformin should be avoided in individuals with significant (moderate-to-severe) renal dysfunction, due to the increased risk for potentially fatal lactic acidosis. An appropriate alternative therapy should be initiated, regardless of gadolinium administration.

Nucleoside analogs, used for the treatment of HIV and hepatitis, are also associated with lactic acidosis. Given that temporary discontinuation of these agents could cause resistance and no cases of NSF associated with their use have been reported to date, withholding these agents does not appear to be the most reasonable option. However, it may be prudent to evaluate acid–base balance in patients on nucleoside analogs and correct any imbalances prior to gadolinium administration.

The currently proposed revisions to the Joint Commission Medication Management standard 4.10 indicate that "all prescriptions or medication orders be reviewed by a pharmacist for appropriateness."[19] (The Joint Commission specifically includes contrast agents in its definition of medication.) Many pharmacists are not as familiar with gadolinium-based contrast agents used for MRIs as they are with other traditional contrast agents used for X-ray or other imaging procedures.

Summary

The information presented here can help pharmacists, radiologists, imaging professionals, and other healthcare providers become more aware of risk factors associated with gadolinium-induced nephrogenic systemic fibrosis, allowing for more informed decisions regarding the appropriateness or inappropriateness of gadolinium administration and safer policy and protocol development.

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Factores de Riesgo para Desarrollar Fibrosis Sistémica Nefrogénica Inducida por Gadolinio.

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EXTRACTO

OBJETIVO: Identificar los medicamentos y otros potenciales factores de riesgo, además de la disfunción renal, para desarrollar fibrosis sistémica nefrogénica inducida por gadolinio.

FUENTES DE DATOS: La información se obtuvo de PubMed, *International Pharmaceutical Abstracts*, Iowa Drug Information Service, y Google Scholar utilizando los términos de búsqueda: nephrogenic systemic fibrosis, NSF, nephrogenic fibrosing dermopathy, NFD, gadolinium, gadodiamide. gadoversetamide, gadopentetate, gadobenate, y gadoteridol. También se obtuvo información de la Food and Drug Administration y de los fabricantes de los mencionados productos. La recogida de datos se efectúo entre abril y mayo de 2007.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se evaluaron todos los artículos y la información obtenidos. En la revisión se incluyeron además de artículos, otra información como datos referentes a medicaciones y enfermedades concomitantes y otros factores de riesgo para desarrollar fibrosis sistémica nefrogénica inducida por gadolinio, así como guías de práctica clínica.

SÍNTESIS DE LOS DATOS: La fibrosis sistémica nefrogénica (NSF) es un trastorno severo y misterioso que aparece en individuos con insuficiencia renal severa. Prácticamente todos los casos de NSF se han asociado con la administración de medios de contraste con gadolinio. Sin embargo, no todos los pacientes con insuficiencia renal que reciben gadolinio desarrollan NSF. Por lo tanto, se ha sugerido la existencia de otros factores de riesgo. Estos factores de riesgo incluyen medicamentos que podrían causar transmetalación del gadolinio o que podrían producir acidosis, así como altas dosis de eritropoyetina. Los trastornos concomitantes que pueden también predisponer a NSF son hiperfosfatemia, acidosis, cirugía reciente, enfermedad hepática, hipercoagulabilidad, y procesos proinflamatorios.

CONCLUSIONES: Deben evitarse los contrastes con gadolinio en pacientes con insuficiencia renal importante salvo que los beneficios superen claramente a los riesgos. Si se precisara utilizar gadolinio, no deben emplearse quelatos lineales no iónicos (Omniscan y OptiMARK). Debe verificarse de forma proactiva la existencia de enfermedades y tratamientos concomitantes que puedan aumentar el riesgo de NSF en los individuos con insuficiencia renal que requirieran gadolinio y debe ajustarse a la terapia a esas circunstancias.

Traducido por Juan del Arco

Les Facteurs de Risque Associés au Développement de la Fibrose Néphrogénique Systémique Induite par le Gadolinium

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RÉSUMÉ

OBJECTIF: Revoir les facteurs de risque et les médicaments pouvant favoriser le développement d'une fibrose néphrogénique systémique (FNS) suite à l'utilisation de gadolinium.

SOURCE DE L'INFORMATION: Une recherche a été effectuée dans les banques de données PubMed, *International Pharmaceutical Abstracts*, Iowa Drug Information Service, et Google Scholar avec les mots-clés suivants: fibrose néphrogénique systémique, dermopathie néphrogénique fibrosante, les acronymes NSF et NFD (abréviations anglophones pour les termes Nephrogenic Systemic Fibrosis et Nephrogenic Fibrosing Dermopathy), gadolinium, gadodiamide, gadoversétamide, gadopentétate, gadobénate, et gadotéridol. Certaines informations ont aussi été obtenues directement de l'agence réglementaire américaine et des fabricants des différents produits cités précédemment. L'information a été colligée entre les mois d'avril et de mai 2007.

SÉLECTION DE L'INFORMATION: Toute la documentation identifiée par les différentes stratégies de recherche a été évaluée. Les articles et les autres sources d'information qui faisaient mention des thérapies concomitantes, des conditions médicales et des facteurs de risque pouvant favoriser le développement d'une FNS ont été inclus dans cette revue. Les lignes de pratique clinique quant à l'administration des substances de contraste contenant du gadolinium ont aussi été revues.

RÉSUMÉ DES DONNÉES: La FNS est une condition sérieuse se manifestant chez les patients souffrant d'insuffisance rénale sévère. Presque tous les cas de FNS ont été associés avec l'administration de substances de contraste contenant du gadolinium. Toutefois, tous les patients insuffisants rénaux ayant reçu une telle substance ne développent pas cette toxicité rénale, suggérant ainsi la présence de facteurs de risque additionnels. Ces facteurs de risque incluent notamment l'utilisation de hautes doses d'érythropoïétine ou de médicaments pouvant causer une acidose ou pouvant altérer le complexe gadolinium-ligand dû à la présence d'ions métalliques bi- ou trivalents (e.g. multivitamines, fer, zinc, cuivre, calcium). Plusieurs conditions médicales tels qu'une hyperphosphatémie, une acidose, une chirurgie récente, une maladie hépatique, un processus inflammatoire ou une condition favorisant une hypercoagulabilité peuvent aussi prédisposer un patient à développer une FNS.

CONCLUSIONS: Les substances de contraste contenant du gadolinium devraient être évitées chez les patients insuffisants rénaux sévères à moins que les bénéfices reliés à l'utilisation de telles substances dépassent clairement les risques potentiels. Si toutefois l'utilisation de gadolinium s'avérait nécessaire chez cette population, les formulations de gadodiamide (Omniscan) et de gadoversétamide (OptiMARK) seraient à proscrire préférentiellement. Les patients insuffisants rénaux nécessitant l'administration de gadolinium devraient être investigués de façon proactive pour toute condition médicale pouvant favoriser le développement d'une FNS. Une histoire médicamenteuse détaillée devrait aussi être effectuée pour ces mêmes raisons et des modifications aux régimes usuels pourraient être considérées à la lumière de ces différentes informations.

Traduit par Sylvie Robert