Gadolinium-Containing Contrast Agents and Nephrogenic Fibrosing Dermopathy/Nephrogenic Systemic Fibrosis

The Food and Drug Administration (FDA) first released an alert in June 2006 to healthcare professionals about reports of nephrogenic fibrosing dermopathy (NFD) or nephrogenic systemic fibrosis (NSF) being associated with exposure to contrast agents containing gadolinium. This report was updated in December 2006, citing over 90 cases of NFD/NSF reported to the FDA. There are currently 5 gadolinium-containing contrast agents approved by the FDA for use in magnetic resonance imaging (MRI). These include OptiMARK, Omniscan, Magnevist, MultiHance, and ProHance. The majority of cases reported to the FDA have been with the use of Omniscan, although there have been reports of NSF with the use of OptiMARK and Magnevist. Magnetic resonance angiography (MRA) may also involve the use of gadolinium-containing contrast agents. However, the dose of contrast agent used in MRA procedures may be up to 3 times higher than the dose approved by the FDA for the use in MRI. The normal half-life of gadolinium-containing contrast agents is approximately 1.5 hours, although it may exceed 30 hours in patients with chronic renal failure. When gadolinium is present in its free ionic state, it may precipitate with anions and form depositions.

Nephrogenic fibrosing dermopathy is a condition predominantly affecting the skin that was first described in 1997. NFD results in hardening of the skin and development of plaques affecting the buttocks, trunk, and extremities. It is diagnosed by skin biopsy. After initial recognition of the condition, it was noticed that NFD may also have systemic involvement, resulting in the condition being termed “nephrogenic systemic fibrosis” (NSF) to reflect this potential for systemic involvement. The terms NFD and NSF are now used interchangeably to describe the same condition. Fibrotic changes can be seen in the heart, lungs, skeletal muscles, and other organs. These systemic effects have resulted in an increased risk of thrombotic events, renal tubular fibrosis and calcification, myocardial fibrosis, tendon thickening, fibrosis of the lungs, and fibrosis and calcification of the diaphragm. Other systemic symptoms reported include muscle weakness, pruritus, and overall pain. In more severe cases of skin involvement, joint immobility can occur and impair ambulation. The etiology of NFD/NSF is still unknown at this time. There is no known cure for this condition and it may be fatal, although with a less than 5% incidence. It is most commonly reported in patients with end-stage renal disease who require dialysis.

Literature Review
The Centers for Disease Control and Prevention (CDC) and Missouri Department of Health and Senior Services received a report of NFD cases involving patients undergoing dialysis at a St. Louis hospital. This report was submitted by nephrologists at that hospital in May 2006. An investigation yielded 33 patients with NFD in St. Louis, of which, 28 were found in the reporting hospital between December 2002 and August 2006. There were 25 cases confirmed by both skin biopsy and clinical findings, and the remaining 3 cases were suspected on the basis of either skin biopsy results or clinical findings. Five additional cases were also discovered, but these patients had limited data available about them and thus were not included in the analysis. Three controls were selected for each of the 19 cases who were eligible for inclusion into the study. Both control and case subjects were required to have information documented in their medical record for at least 3 of the 56 months prior to the date of inclusion in order to be eligible for the study. Controls who were selected had received dialysis at the same dialysis clinic on the same day the study subject was diagnosed. The control subjects were eligible for inclusion if they had at least 6 months of renal insufficiency (defined...
as serum creatinine > 2.5 mg/dL) or underwent dialysis for 4 weeks prior to the study date. There were 19 case subjects and 57 control subjects included in the final analysis. There were no significant differences found between the case and control groups on the basis of gender, primary type of dialysis, months since first dialysis session, presence of diabetes mellitus, and the number of days hospitalized as an inpatient in the prior year. A history of exposure to gadolinium-containing contrast agents within 6 months or 1 year prior to study enrollment was found on univariate-matched analysis to be associated with the development of NSF. There were significant differences observed between the study and control groups on the basis of history of hypoparathyroidism, history of deep vein thrombosis, edema, and age. When these variables were controlled for, the presence of gadolinium-containing contrast agent exposure in the prior 6 months (odds ratio (OR)=6.11; 95% confidence interval (CI) 1.92 to 19.52; univariate analysis) or prior 1 year (OR=8.97; 95% CI 1.28 to 63.01; multivariate analysis) was still statistically significantly associated with the development of NSF. Five of the study patients had not been exposed to gadolinium-containing contrast agents in the prior year; however, 4 of these subjects had been exposed to gadolinium in the prior 16 to 68 months. There was one remaining study subject who had no identified prior exposure to gadolinium-containing contrast agents. Study patients with a history of gadolinium exposure in the year prior to diagnosis had increased rates of peritoneal dialysis (versus hemodialysis) and increased time since first dialysis session.

Additional cases have been reported in the literature describing occurrences of NFD/NSF following exposure to gadolinium-containing contrast agents. The time to symptom onset has ranged from 2 weeks to 2 months following gadolinium exposure. These cases have been described both in patients who were and were not receiving dialysis prior to the exposure. Some of the patients who developed NFD/NSF were found to have metabolic acidosis or an elevated anion gap. However, the significance of these characteristics on the development of NFD/NSF is unknown. An additional case report resulted in the detection of gadolinium in blood vessels that had a deposition of calcium phosphate in a patient with NFD. This association between gadolinium deposition and calcium phosphate deposition has been proposed to be a potential factor in the development of NSF.

**FDA Guidelines**

The FDA has issued an Information for Healthcare Professionals document regarding the use of gadolinium-containing contrast agents. It recommends that patients with moderate to end-stage renal disease (defined as GFR < 60 mL/min/1.73m²) undergo a risk-benefit analysis regarding the use of gadolinium-containing contrast agents. An alternative agent or imaging procedure should be considered when available. It also recommends the initiation of dialysis in patients with moderate to end-stage renal disease soon after receiving a gadolinium-containing contrast agent for MRI or MRA to help eliminate systemic gadolinium. It is recommended that clinicians educate themselves and also their patients about the presentation of NFD/NSF so that they may quickly recognize its development.

Any healthcare professionals at UIMCC who become aware of possible cases of NFD/NSF are urged to report the adverse effect to the medical center and contact the FDA via MedWatch at 1-800-FDA-1088 or by accessing [http://www.fda.gov/medwatch/index.html](http://www.fda.gov/medwatch/index.html).

**Centers for Disease Control and Prevention Update: Gonococcal Infections – April 2007**

The Centers for Disease Control and Prevention (CDC) has issued an update to its 2006 treatment guidelines for sexually transmitted diseases regarding the treatment of gonococcal infections. Fluoroquinolones are no longer recommended for the treatment of these infections due to a steady increase in the number of resistant *Neisseria gonorrhoeae* isolates.

Susceptibility of *N. gonorrhoeae* isolates is monitored nationally through the Gonococcal Isolate Surveillance Project. Samples are collected from men who attend various clinics in the United States. Isolates are considered resistant when the minimum inhibitory concentration (MIC) to ciprofloxacin is ≥ 1 mcg/mL. The CDC and World Health Organization use a 5% cut-off value when recommending therapy for gonorrhea; therefore, if the prevalence of resistant isolates reaches 5%, the treatment is no longer recommended. Fluoroquinolone-resistant gonococcal isolates have been identified since the 1990s, and in 2000 fluoroquinolone therapy was no longer recommended to treat gonorrhea acquired in Asia or the Pacific Islands. In 2004, this was expanded to California and for men who have sex with men. Resistance has continued to spread and has now reached a prevalence of 6.7% among heterosexual males and 38.3% for men who have sex with men (2006 data through June).

Now that the threshold has been reached, CDC no longer recommends the use of fluoroquinolones for treating gonococcal infections. Cephalosporins (ceftriaxone and cefixime) are the only class of antibiotics currently recommended for first-line therapy of gonococcal infections. Notably, cefixime tablets are not available in the United States today. Alternative therapy depends on the site and severity of the infection and may include spectinomycin, another therapy not available in the United States. Patients unable to take cephalosporins have extremely limited options for therapy and should be managed by a specialist. The updated recommendations for treating gonococcal infections are presented in the table on page 3.
### Table. CDC recommendations for management of gonococcal infections.*

<table>
<thead>
<tr>
<th>Infection</th>
<th>Recommended Regimens</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated (cervix, rectum, and urethra)</td>
<td>Ceftriaxone 125 mg IM x 1 or Cefixime 400 mg orally x 1</td>
<td>Spectinomycin 2 g IM x 1 (Not available in US) or Single-dose cephalosporin regimens**</td>
</tr>
<tr>
<td>Uncomplicated (pharynx)</td>
<td>Ceftriaxone 125 mg IM x 1</td>
<td>N/A</td>
</tr>
<tr>
<td>Disseminated***</td>
<td>Ceftriaxone 1 g IM or IV every 24 hours</td>
<td>Cefotaxime 1 g IV every 8 hours or Ceftizoxime 1 g IV every 8 hours or Spectinomycin 2 g IM every 12 hours (Not available in US)</td>
</tr>
</tbody>
</table>

*Concurrent azithromycin or doxycycline should be given for chlamydial infections if not ruled out.  
**Ceftizoxime 500mg IM; or cefoxitin 2g IM, administered with probenecid 1g orally; or cefotaxime 500mg IM.  
***Intravenous therapy is recommended for 24 to 48 hours after clinical improvement.

In addition to the above recommendations, fluoroquinolones have been removed from treatment recommendations for pelvic inflammatory disease and restricted to patients with negative gonococcal cultures being treated for epididymitis.

The increased prevalence of fluoroquinolone-resistant *N. gonorrhoeae* isolates leaves clinicians with limited treatment options for patients with gonococcal infections. Clinicians can monitor the availability of cefixime and spectinomycin by visiting [http://www.cdc.gov/std/gonorrhea/arg](http://www.cdc.gov/std/gonorrhea/arg).

**Food and Drug Administration Update – Withdrawal of Pergolide and Tegaserod**

At the end of March, the Food and Drug Administration (FDA) announced the withdrawal of 2 marketed drugs, pergolide (Permax) and tegaserod (Zelnorm). Pergolide, a dopamine agonist used in the treatment of Parkinson's disease, was voluntarily withdrawn by its manufactures due to the risk of valvular heart disease associated with its use. The risk has been identified in post-marketing surveillance and confirmed in recent literature. FDA will work with manufactures of pergolide to determine the feasibility of issuing an investigational new drug application (IND) to allow for use in patients who are not adequately treated with other agents.

FDA asked Novartis to stop selling tegaserod in light of cardiovascular side effects identified with the drug including myocardial infarction, angina, and stroke. The data for these side effects are based on results of Novartis’ analysis of 29 short-term, randomized, controlled trials. Thirteen patients treated with tegaserod developed these effects (0.1%) compared to 1 placebo recipient (0.01%). Based on these numbers, FDA concluded that the benefit of treatment does not outweigh the risk for the majority of patients. FDA and Novartis are working on mechanisms to provide tegaserod to patients in whom the potential benefit outweighs these risks.

**P&T Committee Formulary Action**

**Additions**
- Sevelamer
- Rotavirus vaccine
- Tetanus-diphtheria-acellular pertussis (Adelcel®) vaccine

**Deletions**
- Pergolide
- Measles vaccine
- Mumps vaccine

**Authors:**
Kristen Felice, PharmD  
Amy Lodolce, PharmD, BCPS

**Editor:**
Amy Lodolce, PharmD, BCPS