Foreword to the English version of "Guidelines for Administering Gadolinium Based Contrast Agents to Patients with Renal Dysfunction"

On July 25th, 2008, the Joint Committee for NSF and Use of Gadolinium Based Contrast Agents (Japan Radiological Society, Japanese Society of Nephrology) announced the "Guidelines for Administering Gadolinium Based Contrast Agents to Patients with Renal Dysfunction." These guidelines were revised to reflect various opinions and recent research, and presented as the revised version of the guidelines on September 2nd, 2009. This is an English translation of the revised version.

Considering the volume of GBCAs used, the number of reported NSF cases in Japan compared to that of other countries has been quite small (fewer than 20 confirmed cases, with no new NSF cases reported). These guidelines need to be enforced to continue this trend and to remind the medical community of the lesson learned from the tragedy of NSF.

The purpose of presenting this English version of the guidelines is to clarify NSF prevention procedures in Japan to practitioners outside the country. If there is any inconsistency or ambiguity between the English and Japanese versions, the Japanese version shall prevail.

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Guidelines for Administering Gadolinium Based Contrast Agents to Patients With Renal Dysfunction

Joint Committee for NSF and Use of Gadolinium Based Contrast Agents
(Japan Radiological Society, Japanese Society of Nephrology)

Introduction

Nephrogenic Systemic Fibrosis (NSF) has been associated with the use of gadolinium based contrast agents (GBCAs) in patients with serious renal dysfunction. NSF is a disease

characterized by swelling, hardening, and pain of the skin and subcutaneous tissues after administration of GBCAs. Symptoms may develop over a period of days, months and occasionally years after exposure to GBCAs. Disease progression can lead to limb contractures, severely limiting physical activity. There is currently no known cure, and there have been reports of death due to complications of NSF.
These guidelines have been prepared in order to prevent further cases of NSF. We recommend adoption of the following guidelines.

Text

1. Regardless of renal function, GBCAs should be used only when absolutely necessary for adequate diagnosis. When administered, there must be strict adherence to the indications and dosage stated in the respective drug's package insert. GBCAs should never be used as a contrast agent for X-ray examinations such as CT or angiography.

2. Before performing a contrast enhanced MRI, renal function (glomerular filtration rate, GFR) should be evaluated except in emergency situations. In the clinical setting, it is recommended this be done by calculating the estimated GFR (estimated glomerular filtration rate, eGFR) based on the patient's gender, age and serum creatinine level (Notes 1). The serum creatinine level should be as recent as possible.

3. When the following pathology is present, a GBCA enhanced MRI should be replaced with an alternative examination:

- End-stage renal dysfunction in long-term dialysis patients
- Chronic renal failure with GFR less than 30mL/min/1.73m^2 in non-dialysis patients
- Acute renal failure

4. When any of the pathologies listed in 3 apply but use of a GBCA is absolutely necessary, it is preferable to avoid GBCAs for which there are many reported cases of NSF (Notes 2).

5. There are those who argue that for GFR greater than 30 mL/min/1.73m^2 but less than 60mL/min/1.73m^2, the risk of developing NSF after exposure to GBCA is not necessarily high. However, as there have been reports of such patients developing NSF, the risks and benefits of a GBCA enhanced MRI should be carefully considered before the administration of a GBCA. If the exam is to be performed, the minimum required dose should be used

(Notes 2).

6. When GFR exceeds 60mL/min/1.73m^2, there is little evidence suggesting high risk for developing NSF after use of GBCAs.

7. GBCAs should not be used in patients in whom NSF has already been diagnosed.

8. NSF and its relationship to GBCAs have yet to be completely understood. These guidelines are based on what is currently known. As more is learned about this disease, these guidelines will be revised appropriately.

Notes

1. Notes on eGFR

1) The following formula should be used for Japanese adults.

Males: eGFR (mL/min/1.73m^2) = 194 x $Cr^{-1.094}$ x $Age^{0.287}$

Females: eGFR (mL/min/1.73m^2) = 194 x $Cr^{-1.094}$ x $Age^{0.287}$ x 0.739

2) As renal function is unstable in acute renal failure, eGFR is not a reliable indicator.

3) The formula for estimating GFR is intended for adults and is not intended for patients younger than 18 years old.

4) This formula should not be used for pregnant patients (there is no data for measured GFR during pregnancy).

5) The accuracy of eGFR is limited. 75% of cases will have a measured GFR within 30% of eGFR. When precise evaluation of renal function is needed, GFR (inulin clearance) or Ccr (creatinine clearance) must be measured. As Ccr is greater than GFR, it should be corrected by x0.715 and adjusted for the standard body surface area (1.73 m^2)

6) When creatinine production is decreased, for example, in patients with muscle atrophy (disuse atrophy in bedridden patients, muscular dystrophy, polymyositis, and amyotrophic disease such as amyotrophic lateral sclerosis), GFR will be greater than actual renal function.

7) In patients with extreme body habitus, malnutrition, fluid retention such as edema, pleural effusion and ascites, there may be a larger margin of error.

8) The following regarding changes in serum creatinine should be taken into consideration.

(1) Serum creatinine fluctuates 10% daily.

(2) Serum creatinine increases with strenuous exercise and large amounts of meat consumption, and decreases when protein intake is limited.

(3) Cimetidine and trimethoprim decrease creatinine excretion through the renal tubules and potentially increase serum creatinine.

2. Reliably estimating the probability of developing NSF is not simple, and the difference in risk of NSF among the various GBCA is unclear. However, from the available data, it appears that Gadodiamide（Omniscan）has the largest number of reported cases, and it is estimated that 5% or fewer renal dysfunction or dialysis patients who received Gadodiamide developed NSF. Gadopentetate dimeglumine（Magnevist）has the second most reported cases. There are almost no reported cases of NSF for Gadoteridol（ProHance）and Gadoterate（Magnescope）.

3. Possible factors that may increase the probability of developing NSF are large doses or

repeated administration of GBCAs. Extensive tissue injury (active infection, arterial and venous thrombosis, major surgery), patients with reduced renal dysfunction who have received or are awaiting liver transplants, and simultaneous use of erythropoietin have also been reported as potential exacerbating factors.

4. When there is fluid collection in the body, such as in pregnancy (amniotic fluid) and ascites, GBCAs may possibly be retained in the body for long periods in these fluids, and therefore use of GBCAs warrants caution.

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