

Editor's Note: Adverse drug reactions experienced by HMC, SCCA, or UWMC patients and reported via Patient Safety Net (PSN) are reviewed quarterly by the UW Pharmacy & Therapeutics Committee. Following the Committee's review, a literature-based companion article regarding some aspect of adverse drug reactions is published in this newsletter. It is hoped that these articles will be useful tools to remind prescribers of the fundamental principle of pharmacology that states, "No drug has only one action." By reminding prescribers to be alert to the appearance of undesired and unintended actions of drugs, therapeutic outcomes may be improved and adverse events minimized. If you have a patient you feel is experiencing an Adverse Drug Reaction, please report it via Patient Safety Net.

ADR Focus by Elizabeth Rudy, DVM, RPh

Spotlight on Intravenous Immune Globulin Therapy and Acute Renal Failure

A 57-year-old man comes into the emergency room of a local hospital complaining of progressive shortness of breath and increasing nausea and anuria over the past two days. His medical history includes polymyositis, hypertension, mild renal insufficiency, anemia, and hypertrophic cardiomyopathy. Four days prior to the onset of his symptoms, he was seen in the hematology clinic where he received a first course of IVIg therapy for treatment of polymyositis. The man's laboratory and urine analyses on admission to the hospital indicate that he is suffering from acute renal failure most likely attributable to his recent therapy with a sucrose-containing IVIg formulation. On day 1 of his hospital stay, the man's serum creatinine peaks at 9.4mg/dL and his blood urea nitrogen (BUN) level peaks at 85mg/dL. His urine output is less than 100mL/hour. He is treated with torsemide to increase urine output, calcium acetate for hyperphosphatemia, and sodium polystyrene sulfonate for hyperkalemia. By day 3 of hospitalization, the man's respiratory status shows significant improvement and his renal function test values start trending downward. On day 6 of hospitalization, he is discharged with a serum creatinine of 5.9mg/dL and a BUN of 82mg/dL. His urine output is well maintained. Two days later, when the man is evaluated in the renal clinic, his serum creatinine and BUN levels are 2.3mg/dL and 64mg/dL respectively, and he is doing well.¹

Intravenous immune globulin (IVIg) was first licensed in 1981 by FDA and is considered a mainstay of therapy for primary immunodeficiencies, immune-mediated thrombocytopenia, Guillain-Barre' syndrome, Kawasaki syndrome, pemphigus, chronic B-cell lymphocytic leukemia, and HIV infection. Additionally, it is estimated that in clinical practice, IVIg has been used to treat between 50 and 60 other medical disorders, including its use as prophylaxis for infections and for prevention of graft-versus-host disease in organ transplant patients.^{1,2}

IVIg is a sterile, purified immunoglobulin G (IgG) preparation made from pooled human plasma and stabilized with glucose, maltose, sucrose, sorbitol, glycine, or albumin. Overall, the incidence of adverse effects following administration of IVIg ranges from 1-15%.³ Common reactions including pain, fever, chills, and fatigue, tend to be related to the rate of product infusion, and are usually mild-to-moderate in severity and self-limiting.^{1,3} These reactions are probably caused, in most cases, by the formation of immunoglobulin aggregates during the production or storage of IVIg preparations.³ To avoid aggregate formation and reduce the frequency and severity of adverse reactions, the purified immunoglobulin products are stabilized with one of the above sugars, glycine, or albumin.

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IVIg is a sterile, purified immunoglobulin G (IgG) preparation made from pooled human plasma and stabilized with glucose, maltose, sucrose, sorbitol, glycine, or albumin.

Adverse reactions to IVIg (including pain, fever, chills and fatigue) are probably caused, in most cases, by the formation of immunoglobulin aggregates during the production or storage of IVIg preparations. To avoid aggregate formation and reduce the frequency and severity of adverse reactions, the purified immunoglobulin products are stabilized with sugar, glycine, or albumin.

In 2005, Itkin and Trujillo reported that FDA had received over 114 reports worldwide of acute renal failure associated with IVIg therapy. Seventeen deaths, primarily among patients with other serious underlying medical conditions, occurred in the reports received by FDA.

The association between IVIg administration and acute renal failure was first identified in 1987.⁴ In 2005, Itkin and Trujillo reported that FDA had received over 114 reports worldwide (with 87 reports in the United States) of acute renal failure associated with IVIg therapy.¹ Seventeen deaths, primarily among patients with other serious underlying medical conditions (such as sepsis, pneumonia, or cardiac insufficiency) were noted in the reports received by FDA.^{1,2} The incidence of IVIg-associated acute renal failure is difficult to determine. The extent of underreporting of this adverse effect is unknown. However, the large number of patients who receive IVIg therapy annually combined with the few reported cases, suggest that the overall incidence is probably relatively low.³

A diagnosis of IVIg-associated renal failure is one of exclusion and requires a temporal association between immunoglobulin infusion and the development of acute renal failure.¹ Itkin and Trujillo describe the following clinical presentation for IVIg-associated acute renal failure.¹ Renal insufficiency usually develops within 1 week after initiation of IVIg therapy with serum creatinine levels peaking around day 5. Oliguric renal failure occurs more commonly than nonoliguric renal failure. Fortunately for the majority of patients, renal failure is reversible when the IVIg infusion is discontinued; although about 30% of patients typically require short-term hemodialysis. On average, renal function typically returns to normal within 14 days after the onset of acute renal failure. Despite a positive outcome for the majority of patients, for some, the condition may progress to chronic renal failure or death.

The exact pathophysiology of IVIg-associated acute renal failure remains unclear. Numerous mechanisms have been proposed to account for this adverse effect.^{1,5} The most promising hypothesis (termed “osmotic nephrosis”) holds that vacuolization plus swelling of the renal tubular epithelium occurs secondary to osmotic stress from the sugars used as stabilizers in the IVIg products.¹ This theory is supported by histology of affected renal tissue that shows vacuolization and swelling of the proximal segments of the proximal tubule and to a lesser extent, the glomerular cells.¹ Additionally, these histologic changes resemble the distinctive pathology seen in renal tissue following administration of high doses of sucrose.⁶

Lending further support to the above theory is the fact that the *majority* of cases of IVIg-associated acute renal failure have occurred following the administration of sucrose stabilized products.^{1,6} When given intravenously, sucrose is not enzymatically hydrolyzed, and thus the sucrose molecules must be filtered unchanged at the glomerulus in order to be excreted in the urine. Sucrose could accumulate at the renal tubular epithelium in patients with compromised renal function and result in the histologic changes described above.¹ Janigan and Santamaria showed in a rat study that renal tubular injury may result from the intracellular accumulation of sucrose by pinocytosis.⁷ This intracellular accumulation of sucrose could lead to the osmotic intake of fluid into the cells, resulting in cellular swelling and vacuolization.¹

Interestingly, other sugars used to stabilize IVIg products, such as glucose and maltose, have not been associated with similar rates of acute renal failure.¹ This is most likely due to the fact that renal tubular cells can metabolize these molecules. For example, maltose is digested and metabolized to carbon dioxide by kidney cells.¹ Reports exist of patients who were able to tolerate IVIg treatment with products stabilized with maltose but later developed acute renal failure when treated with sucrose-containing IVIg products.⁶

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In 1999, FDA developed a series of recommendations for proper patient management regarding the administration of IVIg products.

Patient risk factors for acute renal failure following administration of IVIg include the following:^{1,3,6}

- intravascular volume depletion
- sepsis
- preexisting renal insufficiency
- older age (65 years old or above)
- diabetes
- concurrent diuretic therapy or concomitant treatment with nephrotoxic drugs
- large dose sucrose administration
- rapid infusion rate
- use of concentrated IVIg preparations that have not been diluted.

In 1999, FDA developed a series of recommendations for proper patient management regarding the administration of IVIg products. (See Table I) Because the use of IVIg is ever increasing, and because IVIg-associated renal failure is a serious, life-threatening but potentially preventable adverse drug reaction, practitioners need to familiarize themselves with the above guidelines and take them into account when developing treatment strategies for their patients.

Table I: Some Guidelines for the Safe Administration of IVIg Products^{1,3}

⇒	Ensure adequate patient hydration prior to start of IVIg infusion.
⇒	Take extra precaution when administering IVIg products to patients with increased risk factors for acute renal failure. These factors include: preexisting renal insufficiency of any degree; diabetes; age 65 years or older; volume depletion and dehydration; sepsis; paraproteinemia; concurrent treatment with nephrotoxic medications.
⇒	Use the recommended dose of IVIg.
⇒	Dilute IVIg preparations to a concentration that will minimize the rate of delivery of the carbohydrate stabilizer to the kidneys (most important for patients at high risk for development of acute renal failure).
⇒	Decrease the rate of infusion: For the sucrose containing formulations Sandoglobulin and Panglobulin, the maximum infusion rate of IVIg is 2mg/kg/minute and for Gammar-P.I.V. the rate of 3mg/kg/minute should not be exceeded.
⇒	Assess renal function (urine output, serum creatinine, and blood urea nitrogen) before the infusion and at appropriate intervals after treatment. If renal function deteriorates after treatment, consider discontinuing IVIg therapy.
⇒	Limit sucrose-containing formulations to patients with normal renal function. Reserve non-sucrose-containing formulations for patients at risk for development of renal insufficiency.
⇒	Review approved indications for IVIg therapy.

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Pharmacy & Therapeutics Committee Actions

Formulary Additions	Dosage Form(s), Strength(s)*	Therapeutic Classification	Labeled Indication	Usual Adult Starting Dose*
Abatacept (Orencia [®])	Injection: 250mg	Immunomodulator	Rheumatoid arthritis	Weight-based.
	Added to formulary restricted to use for patients who have failed or cannot tolerate therapy with etanercept or infliximab. In addition, the provider must prescribe within the scope of Medicare coverage and obtain prior authorization for patients with private insurance coverage.			
Omeprazole (generic)	Tablet: 20mg	Proton pump inhibitor	Gastric acid suppression	20mg PO Q day.
	Lansoprazole and pantoprazole remain the preferred UW Formulary proton pump inhibitors. Generic omeprazole 20mg tablets were added to formulary restricted to ambulatory patients.			
Rifaximin (Xifaxan [®])	Tablet: 200mg	Anti-infective	Traveler's diarrhea	200mg PO TID X 3 days.
	Added to formulary restricted to use by Hepatology Service for patients with hepatic encephalopathy intolerant or unresponsive to lactulose and/or neomycin.			
Formulary Deletions	Form(s) & Strength(s)	Classification	Comment	
Benzocaine	All	Topical Anesthetic	Replaced by lidocaine or phenol, depending on use.	
	The P&T Committee approved automatic substitution by pharmacy of lidocaine 4% solution or phenol spray based on the indication for use.			
Other Actions				
Amylase-Lipase-Protease	The P&T Committee approved automatic substitution of an equivalent generic for the discontinued Pancrease [®] product.			
Rizatriptan	Maxalt MLT [®] (orally disintegrating tablets) were added to the UW Preferred Drug List (UW-PDF).			

* Refer to product labeling for full prescribing information. *Contact pharmacy for information on drug costs.

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June P&T Committee Actions, 28

Insert: Complementary & Alternative Medicine: Glucosamine & Chondroitin



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drug therapy topics