

Acute Renal Failure Following Intravenous Immunoglobulin Therapy

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Intravenous immunoglobulin (IVIG) has been used as replacement therapy for primary and secondary immunodeficiencies since the early 1950s. Some IVIG preparations contain sucrose, which can cause a rare nephropathy characterized by acute renal failure (ARF) caused by sucrose uptake by renal proximal tubule cells with subsequent cellular swelling and occlusion of the tubular lumen. This article presents the case of an elderly woman with idiopathic thrombocytopenic purpura (ITP) and subsequent ARF due to administration of a sucrose-containing IVIG preparation. Background information on IVIG therapy, adverse effects of immunoglobulin therapy, and pathophysiology, predisposing factors, and prevention of sucrose-related nephropathy are discussed.

CASE PRESENTATION

Initial Presentation and History

A 92-year-old woman with a history of hypertension and hypothyroidism presented to the emergency department with a 1-day history of hematemesis. She described 2 episodes of 100 mL of bright red blood without nausea or abdominal pain. She had no dysphagia or rectal bleeding.

She received 1 day of trimethoprim/sulfamethoxazole (TMP-SMX) therapy for a presumed urinary tract infection found on urinalysis the day prior to admission. She also noted easy bruising with minor trauma for about a month. There was no history of antecedent fevers, chills, or cough, and she had no known allergies. Her medications on admission included aspirin, sertraline, thyroxine, meclizine, and TMP-SMX. There was no history of malignancy, blood dyscrasias, collagen vascular disease, or peptic ulcer disease, and none of her first-degree relatives had any bleeding disorders. The patient was a nursing home resident and quit smoking 15 years ago. She did not consume alcohol.

Physical Examination and Laboratory Evaluation

On physical examination, the patient had a normal temperature (98°F) and heart rate (86 bpm). Her blood

pressure was 150/76 mm Hg (no orthostatic changes). Her conjunctivae were pale and nonicteric. Dry blood was present on her oral mucosa. Chest, heart, and abdominal examinations were normal, and rectal examination was negative. Multiple bruises and ecchymoses were seen on her left upper extremity and the right side of her back. Her initial laboratory values revealed a normal leukocyte count, a hemoglobin level of 8.5 g/dL, a hematocrit of 25.4%, and a platelet count of less than $6.0 \times 10^3/\text{mm}^3$. The mean corpuscular volume was 84 fL. Her electrolyte levels were normal, and her blood urea nitrogen level was 21 mg/dL, with a serum creatinine level of 0.9 mg/dL. Results of a urinalysis were normal. Cardiac enzymes, thyroid-stimulating hormone, and hepatic coagulation and hemolytic profiles (ie, lactate dehydrogenase, haptoglobin, indirect bilirubin) were also normal. Her medications were discontinued, and she was admitted to the intensive care unit.

Clinical Course

On hospital admission, the patient was given 4 U of platelets and 1 U of packed erythrocytes. Antiplatelet antibodies (direct/indirect), antinuclear antibodies, and vitamin B₁₂ and folate levels were obtained. She was started on intravenous (IV) pantoprazole. An abdominal ultrasound revealed no splenomegaly. Despite 4 U of platelets, her platelet count increased to only $9.0 \times 10^3/\text{mm}^3$ by the following day (hospital day 2). A diagnosis of ITP was made and prednisone 1 mg/kg/d in divided doses and IVIG 1 g/kg/d were initiated after consultation with a hematologist on hospital day 3. A significant improvement in her platelet counts was observed; however, her creatinine levels worsened (Table). Urine output was unchanged. Fractional excretion of sodium was

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Table. Sequential Platelet Count and Renal Function of the Case Patient

Parameters	Hospital Day						
	1	2	3	4	7	8	Discharge
Platelet count ($\times 10^3/\text{mm}^3$)	< 6.0	9.0	6.0	44	85	109	114
Blood urea nitrogen (mg/dL)	21	17	12	14	53	63	50
Serum creatinine (mg/dL)	0.9	0.8	0.8	0.9	2.4	1.9	1.1

↑
 IVIG started

↑
 IVIG stopped

greater than 1%. A repeat urinalysis was normal, and a renal ultrasound ruled out obstruction. Her creatinine returned to baseline after IVIG therapy was stopped. After other causes of ARF were excluded, the patient's ARF was presumed to be due to IVIG infusion. The patient was discharged in stable condition after 10 days in the hospital.

DISCUSSION

IVIG has been used as replacement therapy for primary and secondary immunodeficiencies since 1952. It was introduced to treat patients with chronic lymphocytic leukemia. The indications for its use have expanded, and it is now widely used for a variety of immune-related conditions, such as congenital agammaglobulinemia, severe combined immunodeficiency syndromes, common variable immunodeficiency, Wiskott-Aldrich syndrome, ITP, and Kawasaki disease (in combination with aspirin). It has also been effective in treating other conditions such as myasthenia gravis, systemic lupus erythematosus, bullous pemphigoid, severe rheumatoid arthritis, and Guillain-Barré syndrome. IVIG is also used in refractory dermatomyositis/polymyositis and in conjunction with anti-infective therapy to prevent or modify acute bacterial or viral infections in patients with iatrogenic- or disease-associated immunosuppression.¹⁻⁴

In patients with ITP and other autoimmune cytopenias, IVIG binds to Fc receptors on cells within the reticuloendothelial system. IVIG may also lead to reduction in titers of pathogenic antibody, induction or suppression of cytokine production, neutralization of toxins and/or alteration in sensitivity to corticosteroids, and may have effects on apoptosis.⁵

Adverse Effects of Immunoglobulin Infusion Therapy

Adverse reactions caused by immunoglobulin therapy occur in up to 15% of infusions² and include fevers, myalgias, headaches, flushing, chest pain, and shortness of breath. These are caused by activation of the complement cascade by the aggregation of immunoglobulin. To avoid these side effects, stabilizing agents,

such as sucrose, maltose, dextrose, and glycine, are used in conjunction with immunoglobulin. It is common to premedicate patients with acetaminophen and antihistamine to avoid anaphylactic reactions, especially in those suspected of having IgA deficiency. Erythema, pain, phlebitis, and eczematous dermatitis may also occur at the infusion site.^{6,7}

One of the most serious and potentially lethal toxicities of IVIG therapy is ARF. In 1998, the US Food and Drug Administration released a statement elucidating the potential harm associated with use of the immunoglobulins.⁸ In the United States, 83 cases of ARF have been ascribed to the use of IVIG therapy; worldwide reports indicate up to 114 cases, with 17 reported deaths.⁸ Several IVIG preparations with different molecules used as stabilizing agents are available; however, the majority of cases of ARF in the United States have been reported after use of sucrose-containing preparations. Sandoglobulin (Novartis Pharmaceuticals Corporation, East Hanover, NJ) is the most widely used preparation in the United States and contains the largest amounts of sucrose per gram of protein (1.67 g sucrose/1g protein). Another preparation, Panglobulin (ZLB Bioplasma AG, Switzerland) has a similar concentration of sucrose. Of reported renal adverse events in the United States, 69% have been associated with products containing the highest concentration of sucrose.⁸ Twenty-two percent of cases are associated with another product Gammar-IV (Aventis Behring, Kankakee, IL) (1.0 g sucrose/1g protein).⁸ Interestingly, 55% of renal dysfunction involved patients with ITP. Usage of higher and consecutive doses of IVIG therapy for ITP may explain these statistics.⁸

Barton et al⁹ first reported IVIG-associated ARF in 1987 in a case report documenting acute cryoglobulinemic nephritis with deposits of a complex of IgG and a monoclonal IgM paraprotein. Since that initial report, 114 cases of IVIG-related acute renal insufficiency have been documented. The term "osmotic nephrosis" was initially coined in the early 1940s, where it was demonstrated that severe swelling of proximal

epithelial cells occurred in patients who died of renal failure after administration of IV sucrose.^{10,11} Studies performed in experimental animals later revealed that proximal tubular cell swelling could be reproduced by IV infusion of sucrose and mannitol.^{12,13} The temporal association of ARF with sucrose infusion as well as the exclusion of other causes of ARF supported that sucrose was the cause of renal insufficiency.

Sucrose-Related Nephropathy

Sucrose is a disaccharide that yields glucose and fructose on acidic hydrolysis. Certain insects have enzymes that catalyze sucrose hydrolysis to glucose and fructose. In the human kidney, the proximal convoluted tubular (PCT) cells are responsible for reabsorption of filtered carbohydrates, including sucrose. The absorption process involves formation of pinocytic vesicles containing sucrose. After absorption, these vesicles coalesce with lysosomes. Unfortunately, PCT cells cannot hydrolyze sucrose, and accumulation of sucrose inside these cells results in an increased osmotic gradient, prompting water entry into the cells via special water channels observed on the apical cell membrane. The mechanisms thought to underlie the development of renal failure (osmotic nephrosis) with these agents results from cell swelling, vacuolization (causing disruption of cellular integrity), and tubular luminal occlusion from swollen tubular cells.

A similar renal process is observed with parenteral infusion of other filterable macromolecules, such as mannitol, dextran, and radiocontrast agents.¹⁴ Recently, both IVIG and hydroxyethyl starch have been demonstrated to cause this so-called osmotic nephrosis.¹⁵

More than 60% of patients who develop renal failure following IVIG administration are older than age 65 years. Other risk factors include patients with any degree of preexisting renal insufficiency, diabetes mellitus, volume depletion, paraproteinemia, and concomitant use of nephrotoxic drugs. Renal function usually worsens by day 3 to day 10 postinfusion. Most patients are either oliguric or asymptomatic, as in the case patient. Urine sediment is bland and renal biopsy, although diagnostic, is usually not necessary. Although TMP-SMX causes allergic interstitial nephritis, only 1 dose was given to the case patient, and the patient failed to develop eosinophilia, eosinophiluria, or rash. The majority of patients recover completely with appropriate supportive management.

Prevention of IVIG-Associated Nephropathy

Patients should be adequately hydrated prior to initiating IVIG therapy, and physicians should exercise par-

ticular caution while administering IVIG products in patients at increased risk for developing ARF. For sucrose-containing IVIGs, the maximum recommended infusion rate is 3 mg sucrose/kg/min (2 mg Ig/kg/min for Sandoglobulin and Panglobulin; and 3 mg Ig/kg/min for Gammar-IV).⁸

In patients at increased risk for ARF, renal function including urine output, blood urea nitrogen, and serum creatinine should be assessed prior to infusion of IVIG and again at appropriate intervals. Discontinuation of diuretics is also recommended.² Others recommend using dilute IVIG solutions or using other stabilizing agents such as maltose, dextrose, or glycine in high-risk patients.³

CONCLUSION

ARF is a rare complication of IVIG therapy. Acute renal insufficiency occurs within several days after initiation of the infusion. Preexisting renal impairment, volume contraction, and older age predispose to IVIG-induced ARF. Sucrose nephrotoxicity may be minimized with volume repletion before IVIG infusion, discontinuation of diuretics, and slowing the infusion rate and diluting IVIG in hypotonic solution. ARF associated with IVIG therapy is reversible with discontinuation of the infusion and supportive management. **HP**

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