Intravenous immune globulin (IVIG; Gammagard S/D, Baxter Healthcare Corporation, Westlake Village, CA) is a sterile, freeze-dried preparation of highly purified immunoglobulin G derived from large pools of human plasma.\(^1\) The process includes treatment with a solvent and a detergent that provides significant viral reduction.\(^1\) The infusion-related adverse effects of IVIG are fatigue, headache, chills, fever, hypotension, low-back pain or chest pain, and myalgia. These adverse effects are generally self-limiting; however, serious and rare adverse reactions such as thrombotic events, aseptic meningitis, and renal dysfunction can occur.\(^2,3\)

IVIG is currently used as standard treatment in primary immunodeficiency diseases, B-cell chronic lymphocytic leukemia, idiopathic thrombocytopenic purpura, bone marrow transplantation, and Kawasaki disease.\(^1\) IVIG is also used to treat a diverse group of autoimmune neuromuscular disorders that include, but are not limited to, multifocal motor neuropathy, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia, and dermatomyositis.\(^2,3\) The dosage range varies widely in the literature depending on recommendations and indications; typical dosages range from 0.4 g/kg given

\[\text{Case Report:} \]

\[\text{Acute stroke with high-dose intravenous immune globulin} \]

By David A. White and Mandy C. Leonard

**Purpose.** A case of acute stroke in a patient who was receiving high-dose intravenous immune globulin (IVIG) for dermatomyositis is reported.

**Summary.** A 43-year-old woman presented with overwhelming proximal weakness and myalgias, swelling in her hands, facial and knee rash, generalized fatigue, numbness in her left arm, and lower-back pain. Physical examination revealed that she had symptoms consistent with dermatomyositis. The patient was initially treated with prednisone but developed a severe adverse drug reaction to the medication. The prednisone was discontinued, and the patient was admitted to the hospital for a first-time dose of IVIG therapy. During the infusion, the patient was found to have a facial droop, left-sided hemiplegia, and an increase in restlessness. A large, significant right internal carotid artery occlusion was discovered and initially treated mechanically and then with drugs in an attempt to establish revascularization. A subsequent computed tomography scan of the brain demonstrated a large right-middle cerebral distribution infarct with slight hemorrhage into the basal ganglia. IVIG is increasingly being used for many approved and nonapproved indications. Although rare, stroke associated with thrombosis caused by the administration of IVIG has been reported in the literature. On the basis of the Naranjo probability scale, this adverse drug event was calculated as a probable reaction due to the administration of IVIG.

**Conclusion.** A patient had an acute stroke after receiving a high dose of IVIG for dermatomyositis. Patients should be given a slower rate of infusion and smaller dosages of IVIG, and they should be closely monitored for potential stroke associated with thrombosis during IVIG therapy.

**Index terms:** Cerebrovascular accident; Dermatomyositis; Dosage; Drug administration rate; Globulin immune; Injections; Serums; Toxicty

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as a one-time dose to 0.4 g/kg/day given over several days (2-g/kg total dose). Immunomodulatory dosing of IVIG for autoimmune indications are higher and are thought to block the Fc receptors in macrophages that prevent phagocytosis of circulating cells tagged with autoantibodies.⁶⁶

Dermatomyositis is classified as an idiopathic inflammatory myopathy.⁶ Dermatomyositis is a rare disorder in the general population with prevalence rates estimated at around 1 per 100,000 individuals. Its incidence occurs approximately twice as often in women than in men, with the peak incidence in adults occurring in the fifth decade of life. In adults, the survival rate for five years is 75%, and the majority of patients treated (up to 50%) experience long remissions and even recovery.⁷ The most common presenting feature of dermatomyositis is muscle weakness. Most patients develop an elevation of serum levels of lactate dehydrogenase, creatine kinase (CK), aldolase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The presence of muscle weakness, myalgia, heliotrope rash (violaceous eruption of the upper eyelids accompanied by swelling), Gottron’s sign (symmetric, violaceous erythematous eruption on the extensor surfaces of the joints of the fingers, elbows, and knees), and elevated serum levels of muscle enzymes increases the clinical concerns for dermatomyositis. The determining test is muscle biopsy, which establishes the diagnosis of dermatomyositis and rules out other disease states.⁶

**Case Report**

A 43-year-old white woman who had been previously diagnosed with idiopathic neuropathy at the age of 10 years was referred to our institution with overwhelming proximal weakness and myalgias, swelling in her hands, facial and knee rash, generalized fatigue, numbness in the left arm, and lower-back pain. The patient had not been able to drive for the past two months and could not lift her legs, turn over in bed, brush her teeth, or wash her face. A family history revealed that two of her cousins were diagnosed with a neuropathy. Several months earlier, the patient had received a diagnosis of dermatomyositis at another institution and was advised to be treated with IVIG therapy. At that time the patient refused, and she was started on oral prednisone 40 mg/day. When the daily dose of prednisone was increased to 60 mg, the patient developed severe depression secondary to the drug, and it was tapered to 20 mg with rapid worsening of her muscular symptoms. She next began to take 10–15 homeopathic medications in conjunction with chiropractic treatments without any benefit. The patient then decided to proceed with IVIG therapy.

A physical examination on the day of the patient's admission to our clinic revealed progressive weakness, stigmata of Gottron's papules, arthralgias, and peri-orbital edema, all of which were suggestive of dermatomyositis. The patient’s pertinent vital signs were blood pressure, 126/68 mm Hg; heart rate, 84 beats/min; body weight, 100.8 kg; and height, 66 in. She had no other comorbidities consistent with risk factors for stroke (e.g., hypertension, diabetes, previous thrombotic disease). Her selected admission laboratory test results were thyroid-stimulating hormone, 0.131 µunits/mL (reference range, 0.4–5.5 µunits/mL); CK, 4570 units/L (reference range, 30–220 units/L); aldolase, 38 units/L (reference range, 2–8 units/L); AST, 180 units/L (reference range, 7–40 units/L); and ALT, 96 units/L (reference range, 0–45 units/L). An electromyogram showed features consistent with necrotizing myopathy, and a muscle biopsy was ordered. Several days after admission, the findings of chronic inflammation, muscle fiber degeneration and regeneration, and focal areas suggesting perifascicular atrophy were suggestive of dermatomyositis.

The patient was admitted to the general medicine service at 19:30 and was started on oral escitalopram 10 mg/day, oral esomeprazole 40 mg/day, and subcutaneous enoxaparin 40 mg/day. IVIG (Gammagard S/D) was ordered (1 g/kg/day) at 22:00 with acetaminophen 650 mg and diphenhydramine 25 mg as oral premedications. Zolpidem 5 mg was given orally at 01:15 as a one-time dose for sleep. It was documented that diphenhydramine was an allergen to the patient, and it was therefore discontinued. The IVIG infusion (100 g) was started at 02:50 and scheduled to run for four to six hours at a maximum rate of 4 mL/kg/hr. The infusion was stopped at 05:35 when the patient exhibited increasing restlessness, a left facial droop, and left-sided hemiplegia.

The neurology department was immediately consulted because it was suspected that the patient was having a stroke, and it was determined that her National Institutes of Health Stroke Scale score totaled 21, which indicated...
the possibility of a stroke. A computed tomography (CT) scan demonstrated a hyperintense right-middle cerebral artery. The patient was immediately taken to angiography for potential intervention. A significant right internal carotid artery occlusion of the entire M1 segment was discovered, which was subjected to mechanical revascularization. A total of 12 mg of alteplase, 4 mg of abciximab, and 18 mg of eptifibatide were used intravenously for revascularization; however, the M1 segment remained occluded.

The patient was transferred to the neurology intensive care unit (ICU) for further evaluation and care. A transesophageal echocardiogram was performed that demonstrated no significant valvular abnormalities and an ejection fraction of 55% while her blood pressure remained within tight control. The prothrombin time and activated partial thromboplastin time values were both within the normal range. She was then started on oral aspirin 325 mg/day. A hypercoagulable panel demonstrated an elevated immunoglobulin M antiphospholipid antibody titer (i.e., a type of antiphospholipid antibody whose elevation may be indicative of an antiphospholipid syndrome). The factor VIII activity level was elevated as well, and both can be risk factors for thrombosis. It was suggested to recheck these levels in one to two months to see if there was a persistent elevation. However, for this patient, no subsequent testing was done at our institution.

While in the neurology ICU, a subsequent CT scan of the patient’s brain demonstrated a large, right-middle cerebral distribution infarct with a slight hemorrhage into the basal ganglia without midline shift. The patient was discharged nine days later to our skilled nursing unit for rehabilitation. When transferred, she remained sleepy but arousable, spoke minimally, and demonstrated some dysphagia. She intermittently followed commands and grasped with her right upper extremity. The left side was hemiparetic with slight movement of the fingers on occasion. As her clinical status improved, she underwent a magnetic resonance imaging and magnetic resonance angiography of her brain, and the results demonstrated the large right-middle cerebral artery distribution infarct and a small amount of hemorrhage in the right basal ganglia. She progressed relatively well with physical and occupational therapy.

The patient was transferred 23 days later to a skilled facility closer to her home for ongoing continuation of her physical therapy. The patient’s father cancelled the future follow-up appointments with the neurologist and rheumatologist because of transportation-related reasons.

**Discussion**

Dermatomyositis is one of many crippling neuromuscular disorders that can deprive patients of the ability to care for themselves as well as live alone. IVIG has been used for this disorder for years and is one of the safest immunomodulating drugs available for long-term treatment, but adverse drug events can occur. The number of complications being reported is increasing as the use of IVIG expands to new indications. Stroke caused by thrombosis is a rare and infrequent occurrence with IVIG treatment. In a case series (n = 16) by Caress and colleagues, there was a 0.6% proportion of stroke; however, the authors stated that this may be an overestimation because the patients were hospitalized and older and may have had more risk factors for stroke. The majority of events occur during or within 24 hours of the infusion, although strokes may occur at any time during the course of treatment.

The mechanism by which IVIG may cause stroke has not been elucidated, but several theories have been proposed. The first is a confirmed immediate increase in serum viscosity following IVIG infusion that is dependent on the dose. Although this increase may be of no consequence in healthy patients, other patients with preexisting high–normal serum viscosity (e.g., hypercholesterolemia) or risk factors (e.g., carotid artery disease, diabetes mellitus, thrombocytosis) may be at a greater risk of developing a thromboembolic event. This increase in serum viscosity may have an accumulative effect, which may persist in certain patients, thereby explaining delayed thrombosis occurring after several doses. Other unconfirmed explanations may be the activation of platelets by IVIG, contamination of an IVIG product with coagulation factor XI, or passive infusion of antiphospholipid antibodies via IVIG infusion. In addition, therapy with IVIG may cause cerebral vascular spasm leading to ischemia and possible thrombosis, as well as have a direct effect on the vascular endothelium.

The role of IVIG in dermatomyositis was recently assessed in a double-blind, placebo-controlled study, in which IVIG’s role was described as the interruption of complement activation products and the down regulation of several molecules as well as the modification of a number of genes.

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Muscle biopsies showed a statistically significant increase in capillaries and muscle fiber size.12

There has been conflicting information on the potential risk of thrombotic events concerning the dose and rate of administration of IVIG. The Food and Drug Administration (FDA) identifies high-dose IVIG and high infusion rates in susceptible patients as possible risk factors for thrombosis, although exact parameters for the dosage and infusion rate are not specified by FDA.2,3,10 On the basis of reports in the literature, there is also the opposing opinion that strokes are not related to the infusion rate, specific product, or concentration of the IVIG solution (e.g., 5%, 10%).2

Our patient received a 5% concentrated solution of IVIG (Gammagard S/D) following the manufacturer’s infusion protocol of 0.5 mL/kg/hr initially, with a maximum dosage of 4 mL/kg/hr. The exact infusion rate was not documented on the medical administration record or in the clinical notes and, therefore, could not be determined. Because of the early morning administration time, the patient was not as closely monitored, thereby eliminating the chance to closer pinpoint the time of the adverse drug event. On admission, there were not any apparent indications of a preexisting hypercoagulable state. Application of the Naranjo adverse drug reaction probability scale indicated that, in this patient, there was a probable relationship between treatment with IVIG and stroke.13

Despite the rare associations of stroke and IVIG therapy that are documented in the literature, reports are increasingly surfacing with the additional use for off-label indications. Although not a confirmed cause, slower rates of administration and lower adjusted doses (0.5 g/kg/day given initially) using ideal body weight may lead to decreased adverse events. The identification of patients at risk for thrombotic events is also important. Close monitoring of patients receiving IVIG for signs of acute stroke, standard order forms and times, and nurses with specialty training in administration of IVIG should be considered.

Conclusion

A patient had an acute stroke after receiving a high dose of IVIG for dermatomyositis. Patients should be given a slower rate of infusion and smaller dosages of IVIG, and they should be closely monitored for potential stroke associated with thrombosis during IVIG therapy.14

References


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