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Case Presentation

Acute Renal Failure Following Use of Glycine- and Maltose-stabilized IVIG Preparations

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Abstract

Background: Intravenous immunoglobulin (IVIG), used for immunodeficiency and autoimmune conditions, is generally well tolerated but may cause adverse effects such as acute kidney injury (AKI), especially with sucrose-containing formulations.

Case presentation: We present the case of an 83-year-old woman with myasthenia gravis who developed severe AKI following IVIG therapy with sucrose-free products. She was initially treated with glycine-stabilized KIOVIG, followed by maltose-stabilized GENIVIG.

Results: Her serum creatinine increased from 0.70 to 3.78 mg/dL within days, requiring continuous venovenous hemodiafiltration (CVVHDF) for three weeks. The patient had no history of renal disease or exposure to nephrotoxic agents. Given the temporal relationship and absence of other causes, IVIG was identified as the likely contributor.

Conclusion: This case highlights that sucrose-free IVIG preparations may carry a risk of significant nephrotoxicity, warranting close renal monitoring regardless of stabilizer type.

More Information

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Keywords: IVIG; Acute kidney injury; Glycine-stabilised IVIG; Maltose-stabilised IVIG; Myasthenia gravis

Background

Immunoglobulin (Ig) products are derived from plasma pooled from multiple donors. Ig products include intravenous Ig (IVIg), subcutaneous Ig (SCIg), RhD Ig (RhIg), and hyperimmune globulins. Intravenous immunoglobulin (IVIG) preparations contain 16% human serum immunoglobulin and more than 95% IgG, with trace amounts of IgA, IgM, and other serum proteins. Ig preparations are used as replacement therapy in primary and secondary immunodeficiency diseases and as immunomodulators in autoimmune and inflammatory diseases. In immunomodulatory therapy, the generation of idiotypic antibodies, suppression of antibody production, or acceleration of immunoglobulin G (IgG) catabolism are thought to be related to the efficacy of IVIG. In the treatment of neurological autoimmune disorders, mechanisms such as modulation of complement activation and macrophage activity also appear to be involved [1,2]. Zinman, et al. in a randomized study of 51 patients with Myasthenia Gravis (MG), found a beneficial effect of IVIG in patients whose MG worsened [3]. IVIG is typically reserved for patients who do not respond to standard treatment and have refractory MG [4]. During MG flares, the IVIG dose administered over 2 to 5 days generally does not exceed 2 g/kg per month [5]. IVIG-related adverse events are classified as immediate or delayed, depending on their time of onset. Immediate adverse effects include flu-like syndrome, dermatological side effects, arrhythmia, hypotension, transfusion-related acute lung injury, headache, fever, chills, fatigue, anaphylaxis, and bronchospasm [6]. Although some adverse effects occur in fewer than 1% of patients and are considered rare, they can be severe or even fatal [7]. Rare but serious events include aseptic meningitis, acute kidney injury (AKI), hemolysis, thrombotic events, myocardial infarction, and transient ischemic attacks [8].

Case presentation

An 83-year-old female patient with no known

Table 1: Patient Characteristics, IVIG Treatment Details, and Serum Creatinine Levels.

Days	Days 1-4		Day 5	Day 6
IVIG Brand	KIOVIG (a glycine-stabilized IVIG)		GENIVIG (a maltose-stabilized IVIG)	No IVIG treatment (therapy completed)
IVIG Dose (g/kg/day)	0.4		0.4	-
Serum Creatinine (mg/dL)	0.70 (Baseline: before treatment on Day 1)	0.82 (at the end of day 4)	2.92 (at the end of day 5)	3.78 (at the end of day 6. Continuous venovenous hemodiafiltration was initiated.

comorbidities was admitted to the neurology department due to an exacerbation of myasthenia gravis (MG). She was initiated on intravenous immunoglobulin (IVIG) at a dose of 0.4 g/kg/day for five consecutive days, administered through properly controlled infusions. For the first four days, she received KIOVIG, a glycine-stabilized IVIG formulation. Her baseline serum creatinine was 0.70 mg/dL and increased slightly to 0.82 mg/dL on day four. On day five, following a decline in her Glasgow Coma Scale (GCS) score, the patient was transferred to the intensive care unit (ICU), where IVIG was continued with GENIVIG, a maltose-stabilized preparation. Subsequently, her serum creatinine level rose significantly to 2.92 mg/dL. Although IVIG therapy was discontinued the next day, her renal function continued to worsen, peaking at 3.78 mg/dL (Table 1 above).

Continuous venovenous hemodiafiltration (CVVHDF) was initiated due to progressive acute kidney injury (AKI) and sustained for three weeks, prolonging her ICU stay. Given the absence of prior renal dysfunction, lack of nephrotoxic drug exposure, and no identifiable alternative cause, the AKI was attributed to IVIG therapy. As the temporal relationship did not allow a clear distinction between the contributions of the two formulations, both glycine- and maltose-stabilized IVIG products were considered potential culprits.

Discussion

The first case of IVIG-induced acute renal failure was reported in 1987. Between 1985 and 1998, the FDA identified 88 cases of IVIG-induced renal failure, of which 61% were classified as acute renal failure [9] . In 1999, the FDA issued a black box warning on IVIG products in the United States to alert healthcare providers about the risks of acute renal dysfunction, renal failure, osmotic nephropathy, and death associated with IVIG use. From 1999 to 2005, the French National Security Agency of Medicines and Health Products recorded 91 cases of renal failure associated with immunoglobulin infusion. The precise mechanism underlying IVIG-associated renal failure is unclear. Therefore, the literature contains limited information on this topic, especially when considering the data reported in earlier studies . Potential mechanisms include glomerular immune complex deposition, osmotic nephritis, acute tubular obstruction associated with immunologic hemolysis, and transient vascular ischemia due to reduced renal perfusion [10-14]. Known risk factors include diabetes mellitus, existing renal dysfunction, advanced age, volume depletion, sepsis, and paraproteinemia [10,11,15]. The first signs of renal toxicity typically involve elevated BUN or creatinine, followed by oliguria and renal failure, which peak within 5 to 7 days post-infusion. Renal failure may be accompanied by thrombosis, hyponatremia, hyperkalemia and may necessitate dialysis or even kidney transplantation [10,13]. Renal function usually returns to normal after discontinuing IVIG or initiating short-term hemodialysis. However, despite treatment, some patients with immunoglobulin-associated renal failure have progressed to chronic renal failure or have died. Prevention and management of IVIG-associated renal dysfunction include checking renal function before treatment, ensuring adequate hydration, avoiding volume depletion (especially with diuretics), using slower infusion rates, and limiting IVIG to a maximum dose of 0.5 g/kg/day [16]. IVIG preparations differ in their physicochemical properties and composition, which may influence both their clinical efficacy and tolerability [17]. When selecting an IVIG formulation, it is important to consider the patient's immunoglobulin status, kidney function, and potential sensitivities to stabilizers. Therefore, factors such as IgA content, osmolality, and the type of stabilizer should be taken into account. A relationship has been suggested between the development of acute renal failure and the use of IVIG products stabilized with sugars. These sugar-containing products tend to have higher osmolality than sugar-free formulations, such as those stabilized with glycine. Hyperosmolar solutions may lead to fluid shifts during intravenous administration [17]. Of all sugar stabilizers, sucrose is most frequently and strongly associated with IVIG-related renal toxicity [10,17]. Because it is not metabolized in the kidney, sucrose accumulates in the proximal tubules and induces osmotic nephrosis, damaging renal epithelial cells [18,19]. While sucrose-containing IVIG formulations carry a risk of renal toxicity and therefore sucrose-free products are generally preferred, osmotic damage has been rarely reported with maltose-containing IVIG products. [10,11]. Additionally, a case report has demonstrated that renal failure can occur with sucrose-free IVIG formulations stabilized with glycine [20].

Conclusion

While sucrose-containing IVIG products are more frequently linked to nephrotoxicity, this case demonstrates that sucrose-free formulations stabilized with glycine or maltose may also pose a risk of renal impairment. In this patient, renal dysfunction developed during the course of treatment involving both formulations; however, a clear temporal distinction between their individual contributions could not be established. The kidney injury progressed to require continuous venovenous hemodiafiltration

(CVVHDF), leading to prolonged renal dysfunction and an extended intensive care unit stay. Reports of such events remain extremely rare in the literature, particularly in the absence of traditional risk factors and with sucrose-free preparations, making this case a meaningful addition to the clinical understanding of IVIG-associated nephrotoxicity.

Ethics statement

Informed consent was obtained from the patient for publication of this case report and accompanying data.

Author contributions

[DS] conducted the literature review, collected and analyzed the clinical data, interpreted the findings, and drafted the manuscript. [HD] supported the clinical evaluation of the case, contributed to data interpretation, and critically reviewed and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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