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LETTER TO THE EDITORS

Acute encephalopathy in a kidney transplant recipient following infusion of intravenous immunoglobulin

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Dear Sirs,

IVIG products differ in their use of stabilizers, pH, osmolality, and their overall risk profiles including neurological, hematological, renal, pulmonary, and dermatological complications (see Table 1). While most adverse effects secondary to IVIG infusion are attributed to the rate of infusion and the large dose of immunoglobulin itself [1], side effects due to stabilizers have also been described [1,2]. Here, we report a kidney transplant recipient with autosomal recessive polycystic kidney disease (ARPKD) and Caroli disease who developed acute encephalopathy following infusion of a glycine-stabilized IVIG product (Gammagard™ Liquid 10% Baxter Healthcare Corporation, Westlake Village, CA, USA).

An 18-year-old male was admitted for the treatment of antibody-mediated rejection (AMR), status 5 years post deceased donor kidney transplant for ARPKD. He had associated hepatic fibrosis with mildly impaired liver function and significant portal hypertension resulting in recurrent ascites and bleeding esophageal varices requiring transjugular intrahepatic portosystemic shunt placement. He also developed recent ascending cholangitis and new onset diabetes after transplant.

The donor organ was a 0/6 HLA match with no preformed donor-specific antibodies (DSA) detected. The patient went on to develop multiple episodes of biopsy-proven cellular rejection. This admission was precipitated by an acute rise in his serum creatinine to 281 umol/l (baseline 120 umol/l, estimated GFR: 48 ml/min/1.73 m^2). Renal biopsy demonstrated AMR with diffuse peritubular capillary C4d staining, chronic tubular atrophy, interstitial fibrosis (Banff grade 3), and mild cellular rejection (Banff grade suspicious). Given the patient's increased infectious risk, he was treated with IVIG following three daily pulses of IV methylprednisolone.

The patient received 2 g/kg IVIG (110 g total) given over 8 h at a rate of 1.6 ml/kg/h for the first 300 ml and at 2.8 ml/kg/h for the remaining 800 ml. Shortly prior to the end of the infusion, the patient was noticed to be confused. His vital signs were normal, Glasgow coma score was 12/15, and deep tendon reflexes were mildly increased. The remainder of the physical examination revealed mild peripheral edema and ascites, unchanged from previous examination.

Laboratory investigations demonstrated: whole blood sodium 129 mmol/l, plasma sodium 131 mmol/l (139 mmol/l 12 h prior), urea 17.8 mmol/l, creatinine 176 umol/l, and glucose 11.1 mmol/l. Bicarbonate, potassium, calcium, phosphate, magnesium, total protein, serum osmolality, and complete blood count were all normal except for mild thrombocytopenia (stable from previous labs). Serum bilirubin and liver enzymes were normal except gamma-glutamyltransferase was 96 U/l. Albumin and INR were stable at 30 g/l and 1.34, respectively. Tacrolimus trough level drawn the following morning was 5.3 μg/l. Ammonia and glycine levels were significantly elevated at 84 umol/l (normal: 9–33) and 468 umol/l (normal: 158–302) when measured 6 h following the infusion.

Two hours postinfusion, the patient had become more confused. Given the acute drop in plasma sodium, he was started on a normal saline infusion at 40 ml/h and given 40 mg IV furosemide (0.8 mg/kg). His sodium rose to 135 mmol/l 10 h postinfusion, but there was little clinical improvement. Following a normal CT head, lactulose 20 g twice daily was commenced to treat the hyperammonemia. By evening (20 h postinfusion), his cognition had completely returned to normal and examination was unremarkable.

We describe a case of a kidney transplant recipient with ARPKD and Caroli disease who developed acute encephalopathy following a glycine-stabilized IVIG infusion. Hyponatremia, hyperammonemia, and hyperglycinemia were identified, all of which may have contributed to the presentation and each may have been precipitated by the relatively rapid administration of this IVIG product. This case raises concern about the safety of glycine-stabilized IVIG products in patients who have both impaired kidney and liver function.

True hyponatremia and pseudohyponatremia following IVIG infusion have each been reported separately in the

Table 1. Different IVIG products.

Products	Carimune NF	Gammagard S/D	Octagam 5%	Flebogamma 5% DIF	Gammagard Liquid 10%	Gamunex & IGIVnex	Privigen 10%
Stabilizer	5% sucrose	2% glucose	10% maltose	5% sorbitol	0.25 M glycine	0.16–0.24 M glycine	0.25 M L-proline
pH	6.4–6.8	6.4–7.2	5.1–6.0	5.0–6.0	4.6–5.1	4.0–4.5	4.6–5
Na content	0% water 0.9% saline	0.85%	0	<3.2 mM	0	0	0
Osmolality	In sterile water (NS), 3% 192 (498) mOsm/kg; 6% 384 (690) mOsm/kg; 12% 768 (1074) mOsm/kg	5%, 636 mOsm/l; 10%, 1250 mOsm/l	310–380 mOsm/Kg	240–370 mOsm/kg	240–300 mOsm/kg	258 mOsm/kg	240–440 mOsm/kg
Effect on blood glucose	No effect	Increase	No effect Caution: Effect on glucose monitoring in certain glucose meters (falsely high glucose results)	No effect Contraindicated in patients with hereditary fructose insufficiency (sorbitol can metabolize to fructose)	No effect	No effect	No effect Contraindicated in patients with hyperprolinemia due to neurotoxicity
Effect on renal function	Osmotic nephrosis; renal dysfunction; AKI	AKI	Osmotic nephrosis; AKI	Lower risk of AKI comparing with sugar stablizers	Not reported	Not reported	Pigment-mediated AKI 2nd to hemoglobinuria

AKI: Acute Kidney Injury

literature [3,4]. Pseudohyponatremia is a falsely low sodium value that occurs with indirect ion-selective electrode (ISE) methods when elevated proteins or lipids are present. Pseudohyponatremia was unlikely in our patient as his plasma and whole blood samples were measured by direct ISE methods. Furthermore, considering that 1.1 l of hypotonic glycine-based IVIG product (measured osmolality of 260 mOsm/kg) was transfused within 8 h, his consumption of 1.5 l of fluid and a urine output of 500 ml in this period, the hyponatremia was largely due to a dilutional effect.

Hyperammonemia was unexpected in our patient as there were no obvious triggers including gastrointestinal bleeding, sepsis, alkalosis, or hypokalemia. This prompted us to consider glycine as an alternate etiology for our patient's confusion, and we found a significantly elevated glycine blood concentration 6 h after the infusion ended. In the literature, hyperammonemia secondary to glycine metabolism has been recognized in the context of the transurethral resection of prostate (TURP) syndrome. TURP syndrome is a rare life-threatening complication after surgery due to the absorption of glycine-containing irrigation fluid that leads to cardiovascular, neurological, and notable metabolic changes similar to our patient case – hyponatremia, hyperammonemia, and hyperglycinemia [5–7]. TURP syndrome has also been reported in other procedures using glycine irrigation fluid [8]. Hyperammonemia has been observed even in healthy adult male volunteers after intravenous infusion of 1 l of 2.2% glycine over 50 min [9]. The importance of hepatic metabolism in ammonia clearance following a glycine load has been confirmed by animal studies where serum ammonia was significantly greater in cirrhotic rats compared with normal rats after glycine infusion [10].

Lastly, glycine itself may lead to encephalopathy by acting as an inhibitory neurotransmitter, as well as facilitating excitatory transmissions in the brain via *N*-methyl-D-asparate (NMDA) receptors [6]. Glycine toxicity, seen in nonketotic hyperglycinemia, can lead to nausea, vomiting, mild confusion, stupor and coma, severe disorientation and blindness, even in the absence of hyperammonemia. Similar findings were found in patients after TURP with very high plasma glycine values and no signs of ammonia intoxication [5].

In summary, while IVIG therapy is generally considered to be safe, clinicians need to be aware that adverse events may occur due to the combination of IVIG product composition, rate of infusion, and individual patient factors, which current product monographs do not provide warning for. In addition to choosing the most appropriate IVIG product for the individual patient, we recommend in patients with renal and liver dysfunction to transfuse IVIG slowly and to monitor sodium and plasma ammonia levels if there are any neurological changes.

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Conflicts of interest

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