Investigation Into the Viscosity of Commercial IG Preparations

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ABSTRACT

All intravenous immunoglobulin (IVIG) products carry a Boxed Warning for the risks of renal dysfunction and thromboembolic events (TEEs). Patient-related thrombotic risk factors include hyperviscosity, a condition in which increased blood "thickness" heightens the risk of TEEs. Studies have shown that IVIG infusions increase plasma viscosity. To assess whether the viscosity of IVIG products themselves might be a parameter of interest in product selection, particularly for at-risk patients, we undertook an initial investigation into the viscosities of 5 commercially available 10% IVIG products.

Experiments were performed using ALYGLO® (immune globulin intravenous, human-stwk) 10% liquid, GC Biopharma; OCTAGAM® 10% [immune globulin intravenous (human)} liquid, Octapharma; GAMUNEX®-C (immune globulin injection (human), 10% caprylate/chromatography purified), Grifols LLC; PRIVIGEN® immune globulin intravenous (human), 10% liquid, CSL Behring; and GAMMAGARD LIQUID® [immune globulin infusion (human)] 10%, Takeda. IgG content was determined using the Lunatic spectrophotometer (Unchained Labs). Samples were diluted with de-ionized water as necessary to normalize their concentrations for accurate viscosity comparison. Sample viscosities were determined using the Honeybun viscometer (Unchained Labs) at 4, 10, 15, 20, and 25° C. Results were reported in centipoise (cP), a unit of measurement for a fluid's resistance to flow, with a higher cP indicative of greater viscosity.

The results at 25° C were as follows: ALYGLO: 2.506 cP; OCTAGAM: 3.484 cP; GAMUNEX-C: 2.535 cP; PRIVIGEN: 2.698 cP; GAMMAGARD LIQUID: 2.575 cP. For reference, the viscosity of human plasma at 25° C generally ranges from 1.5 to 1.72 cP. All products showed consistent, sequential decreases in viscosity as temperatures increased, suggesting that IVIG infusions at room temperature (25° C) may be a safety consideration for the prevention of TEEs. These preliminary results warrant further investigation to identify potential differences in the viscosities of commercially available IVIG products, which may have implications for product selection in at-risk patients.

BACKGROUND

IVIG treatment has been associated with risk of TEEs, with reported incidence rates ranging from 0.5% to 17%.[1] In 2013, the U.S. Food and Drug Administration (FDA) required a Boxed Warning for all IVIG products outlining this risk. **Figure 1** depicts both patient- and product-related factors associated with increased risk of TEEs with IVIG treatment.

Hyperviscosity is a known risk factor for IVIG-associated TEEs, and it has been established that IVIG infusions increase plasma viscosity–both acutely and cumulatively.[2-4] However, to our knowledge, there haven't been any investigations into the viscosities of IVIG products themselves to determine whether there are differences that may inform product choice, particularly in at-risk patients.

ABBREVIATIONS

cP: Centipoise, a unit of measurement of a fluid's resistance to flow

FDA: U.S. Food and Drug Administration

IVIG: Intravenous immunoglobulin

PKA: Prekallikrein activator

TEE: Thromboembolic event

BACKGROUND, CONT.

Figure 1. Factors associated with increased risk of TEEs[5]

Patient-related

- ✓ Advanced age
- ✓ Prolonged immobilization
- ✓ History of venous or arterial thrombosis
- ✓ Use of estrogens
- ✓ Indwelling vascular catheters
- ✓ Hyperviscosity
- ✓ Cardiovascular risk factors
- ✓ Hypertension
- ✓ Obesity
- ✓ Pregnancy (or postpartum status)
- ✓ Cancer
- ✓ Inflammatory conditions
- ✓ Hypercoagulable disorders

Product-related

- ✓ High doses
- ✓ High infusion rates
- ✓ Presence of contaminants, including:
  - ✓ Activated coagulation factor XI (FXIa)
  - ✓ Antiphospholipid antibodies
  - ✓ Prekallikrein activator (PKA)

PURPOSE

To assess the viscosities of 5 commercially available 10% IVIG products to determine whether viscosity might be a relevant factor in product selection.

METHODS

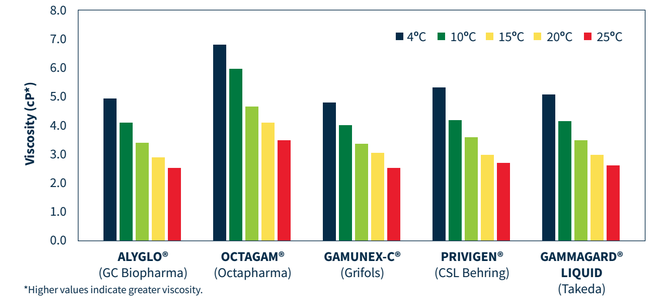
Products tested:

- **ALYGLO®** (GC Biopharma)
- **OCTAGAM®** (Octapharma)
- **GAMUNEX-C®** (Grifols)
- **PRIVIGEN®** (CSL Behring)
- **GAMMAGARD LIQUID®** (Takeda)

1. **IgG content was measured using the Lunatic spectrophotometer (Unchained Labs).**
2. **Samples were normalized for IgG concentration with de-ionized water to ensure accurate comparison.**
3. **Viscosity measurements were performed using Honeybun viscometer (Unchained Labs) at 4°, 10°, 15°, 20°, and 25°C.**

RESULTS

Figure 2. Viscosity assessments



*Higher values indicate greater viscosity.

Table 1. Viscosity assessments

Product	Viscosity (cP)				
	4°C	10°C	15°C	20°C	25°C
ALYGLO® (GC Biopharma)	4.910	4.058	3.391	2.893	2.506
OCTAGAM® (Octapharma)	6.750	5.947	4.658	4.034	3.484
GAMUNEX-C® (Grifols)	4.800	3.997	3.341	3.043	2.535
PRIVIGEN® (CSL Behring)	5.290	4.146	3.537	2.970	2.698
GAMMAGARD LIQUID® (Takeda)	5.080	4.103	3.450	2.964	2.575

All products showed consistent, sequential decreases in viscosity as temperature increased (for reference, the viscosity of human plasma at 25°C ranges from 1.5 to 1.72 cP).

DISCUSSION

This is, to our knowledge, the first study designed to investigate the viscosity of commercially available IVIG products. These preliminary results warrant further investigation to determine whether there are differences in viscosities between products, which may have important clinical implications for product selection in at-risk patients. Because all products showed consistent decreases in viscosity as temperature increased, these data do suggest that room-temperature (25° C) infusions could help mitigate viscosity-related risk.

REFERENCES

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