IVIG Medication Safety: A Stepwise Guide to Product Selection and Use

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Over the past 30 years, intravenous immunoglobulin (IVIG) has been used for the treatment of primary immunodeficiency disorders and numerous autoimmune diseases. During this time, manufacturers have worked to enhance the safety profile of these products, with improvements in purification and stabilization. Additionally, through observation over years of treating patients, clinicians have improved patient tolerability of IVIG therapy. Appropriate selection and use of IVIG products can reduce the rate of IVIG-associated adverse events (AEs). The IVIG safety overview shown in Figure 1, as well as the information presented in Figures 2 through 9 and Tables 1 and 2, is designed to help maximize the safe use of IVIG and to reduce the AEs associated with the infusion of these products.

In some settings, fractionated blood products such as IVIG are stored and distributed by the blood bank, but the majority of institutions handle these products through the pharmacy. Most departments have developed medication use evaluation guidelines that often are evidence-based. Figure 2 models the process in an inpatient hospital setting in which an IVIG order is first reviewed by the pharmacist.

IVIG frequently is divided into 4 categories. First-line use is either FDA- or compendia-approved. Second-line indications have grade B evidence and often are used when first-line therapy has failed or is not

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**Figure 1. IVIG safety overview.**

IgA, immunoglobulin A
tolerated. Third-line indications are restricted to when other therapies have failed, and the evidence for these indications often is limited to open-label studies, small sample sizes, or case reports. Institutions need to develop policies to approve the use of IVIG in these types of indications. Fourth-line indications have no evidence or have evidence that shows that use of IVIG either has anecdotal benefit at best, or is potentially detrimental. IVIG should not be used for these indications. Guidelines from the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology provide further information on the appropriate use of IVIG.¹

### Matching the Right Product

#### To the Right Patient

Clearly, various components contained in an IVIG formulation can affect patients differently. Medical history and patient risk factors, such as contraindications, age, and comorbidities, must be weighed carefully against each product’s criteria to ensure that an appropriate product is selected and severe AEs are avoided. Just as patients receiving IVIG differ, so do IVIG products. Health care providers must make critical clinical decisions as to the appropriate product selection for each patient. Table 1 shows how various IVIG characteristics could affect specific patient risk factors.

### CONTRAINDICATIONS

Some patients have an immunoglobulin (Ig)A deficiency. Most often, this is caused by a failure of the bone marrow or a lack of thymus production of IgA. In more rare circumstances, IgA deficiency is caused by an anti-IgA antibody. In this situation, infusion of IgA could potentially cause anaphylaxis. Normally, this only occurs when the anti-IgA antibody is IgE-derived. Despite the rarity of this occurrence, patients need to be evaluated, and the lowest IgA-content IVIG product should be selected if the benefits of IVIG outweigh the risk associated with its use in such patients (Figure 3).

### AGE CONSIDERATIONS

The effects of age need to be considered when IVIG is being prescribed (Figure 4). Geriatric patients aged...
COMORBIDITIES

Comorbid conditions may determine which IVIG product is most appropriate for individual patients (Figure 5). In patients with diabetes mellitus, the biggest concern is the stabilizer agents used to prevent IgG aggregation. Although glucose directly impacts the insulin requirement, complex sugars such as sucrose and maltose have no impact on these requirements (see Product Features Potentially Affecting Tolerability). Renal insufficiency also should be considered when IVIG products are administered. IVIG-induced renal insufficiency and acute renal failure were first noted with use of IVIG products stabilized with sucrose. This issue can occur with any carbohydrate-stabilized IVIG, and a related “black box” warning is part of all IVIG package inserts. Renal risk factors should be part of the standard review for all patients prior to IVIG product selection. Other safety measures called for in patients with renal insufficiency are using a slow infusion rate and using products that are close to isotonic. Finally, although the exact relationship between IVIG and thrombotic AEs is not fully understood, it is recommended that the infusion rate be slowed, the dose administered during any given infusion be lowered, and isotonic IVIG products be used in patients with a history of thrombotic events or disorders.

PRECAUTIONS

Various other factors require clinicians to use caution when prescribing IVIG (Figure 6).

Aseptic meningitis. Aseptic meningitis is a post-infusion AE. Although the patient with this disorder will exhibit a severe headache with accompanying nuchal rigidity, lumbar puncture will not show evidence of infection. If the patient does not provide information about a previous IVIG administration, the connection might not be recognized. Patient education is imperative. Switching the product may not always result in improvement of this disorder. If the benefit of IVIG therapy outweighs the risk in such patients, use of isotonic IVIG products with a lower dose and rate of administration is warranted.

Hemolysis. Hemolysis is a rare AE associated with IVIG and anti-IgD administration. The exact mechanism and risk factors are not clear. Patients need to be aware of post-infusion signs of hemolysis. Hematuria may cause a darkening of the urine within a few hours of IVIG administration and can serve as an early warning sign of hemolysis.
Figure 5a. Product selection based on comorbidities: diabetes mellitus.

* For more information on false-positive readings with certain monitoring devices, see reference 2.

Figure 5b. Product selection based on comorbidities: renal insufficiency.

Figure 5c. Product selection based on comorbidities: past history of MI, DVT, PE, or thrombotic disorder.

DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism
Sodium considerations. The sodium concentration of IVIG products can vary from 0% to 1.8%. It is important to know the amount and concentration of sodium being infused. Lyophilized products that already have sodium chloride are of particular concern. The choice of diluents is a factor for reconstitution of lyophilized products. Liquid IVIG products normally do not contain sodium chloride.

Transfusion-related acute lung injury (TRALI). This syndrome is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Because TRALI can be associated with significant morbidity and mortality, monitoring for it is important in patients receiving IVIG products.

Volume considerations. If a patient weighing 100 kg receives 1 g/kg of a 5% IVIG, the volume infused would be 2,000 mL. This volume of fluid, especially if hypertonic, could cause numerous problems for patients. Cardiac, pulmonary, and renal dysfunctions cause particular concern. In neonates, because the total blood volume is small, the volume of infused IV fluid can influence the neonate’s metabolic state. Use of higher-concentration yet isotonic solutions of IVIG are best suited for these patients.

Product Features Potentially Affecting Tolerability

In addition to possible clinical efficacy and safety effects, different manufacturing steps also may affect product characteristics that affect tolerability. IVIGs
vary with respect to available formulations, concentrations, osmolalities, IgA content, pH, and sodium and sugar content (Table 2). Some IVIG preparations contain sugar as a stabilizer (Table 2 and Figure 7). Glucose, sucrose, and D-sorbitol also have been used. Other IVIG products do not contain any sugar. Even though sorbitol may not increase the glucose level in the blood, it is metabolized to fructose. Caution needs to be exercised with patients who have hereditary fructose intolerance. A small population of patients may have hyperprolinemia and should not receive products stabilized with L-proline. Volume load (rate of infusion is another factor that can affect tolerability.

**Dosing and Rate Considerations**

**Dosage Selection**

Originally, IVIG was indicated only as replacement therapy for IgG-deficient patients with primary immuno
nodeficiency disorders. Doses ranged from 150 to 250 mg/kg. Evaluation of outcomes and measurement of IgG serum levels revealed that this dose range was suboptimal to achieve an IgG level greater than 600 mg/dL. Doses for replacement therapy usually are in the 400- to 500-mg/kg range, administered every 3 to 4 weeks. For immunotherapy, such as for idiopathic thrombocytopenic purpura and chronic inflammatory demyelinating polyneuropathy, the dosage can be much higher but is normally 2,000 mg/kg per treatment course. If the patient is able to tolerate it, a dosage of 1,000 mg/kg per day for 2 days will result in a rapid response. Some patients may need a lower dosage regimen spread out over time to minimize side effects. Volume considerations must be evaluated with regard to patient age, comorbidities, and so forth (see Figure 8).

**Dosing in Obese Patients**

Clinicians often are concerned with proper dosing of IVIG for patients who are morbidly obese. IVIG product registration studies used actual body weight to calculate the final dose, however, morbidly obese patients usually are excluded from study populations. In most situations, actual body weight should be used, but when the patient’s weight is greater than 100 kg or body mass index is greater than 30 kg/m², an adjustment of dosing weight may be warranted.3

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**Table 2. Pharmaceutical Aspects of IVIG: Osmolality/Osmolarity, Sodium Content, and Stabilizer**

<table>
<thead>
<tr>
<th>Product</th>
<th>Osmolality/Osmolarity</th>
<th>Sodium Content</th>
<th>Stabilizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carimune NF, CSL Behring (lyophilized)</td>
<td>In water: 3%, 192 mOsm/L; 6%, 384 mOsm/L in saline: 6%, 690 mOsm/L; 12%, 1,074 mOsm/L</td>
<td>0%-0.9%, depending on diluent</td>
<td>10% sucrose at 6% concentration</td>
</tr>
<tr>
<td>Flebogamma 5% DIF, Instituto Grifols (liquid 5%)</td>
<td>240-370 mOsm/L</td>
<td>&lt;3.2 mmol/L</td>
<td>5% D-sorbitol</td>
</tr>
<tr>
<td>Gammagard, Baxter Healthcare (liquid 10%)</td>
<td>240-300 mOsm/kg</td>
<td>Trace</td>
<td>No sugar (glycine based)</td>
</tr>
<tr>
<td>Gammagard S/D, Baxter Healthcare (lyophilized)</td>
<td>5%, 636 mOsm/L; 10%, 1,250 mOsm/L</td>
<td>0.85% at 5% concentration</td>
<td>2% glucose</td>
</tr>
<tr>
<td>Gammmaplex, Bio Products (liquid 5%)</td>
<td>480 mOsm/kg</td>
<td>Approximately 40 mmol/L</td>
<td>Sorbitol, glycine</td>
</tr>
<tr>
<td>Gamunex-C, Talecris (liquid 10%)</td>
<td>258 mOsm/kg</td>
<td>Trace</td>
<td>No sugar (glycine based)</td>
</tr>
<tr>
<td>Octagam, Octapharma (liquid 5%)</td>
<td>310-380 mOsm/kg</td>
<td>&lt;30 mmol/L</td>
<td>10% maltose</td>
</tr>
<tr>
<td>Privigen, CSL Behring (liquid 10%)</td>
<td>240-440 mOsm/L</td>
<td>Trace</td>
<td>No sugar (L-proline based)</td>
</tr>
</tbody>
</table>

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*Gamunex-C will replace Gamunex; it is expected to be available by January 2011.*
Figure 7. Considerations for various stabilizers used in IVIG products.

Figure 8. IVIG dose and rate selection steps.

- Doses are customized per patient for maintenance dosing
- For more information on dosing in obese patients, see reference 3.
- See full prescribing information for each product for rate guidelines.

ABW, actual body weight; AE, adverse event; BMI, body mass index; IBW, ideal body weight
RATE DETERMINATION

Each product has a recommended rate of infusion that should be followed. Upon initiation of therapy, an initial rate that allows for observation and monitoring over a 15- to 30-minute period should be used. The rate should be increased as defined and then a third escalation should be instituted to determine the patient’s maximum tolerated rate. AEs can occur at any time, and slowing the rate should be the first consideration. Additionally, the administration of antidotes may be warranted.

On subsequent infusion, specific premedications may be administered to improve patient tolerability. During any situation when slowing the rate does not immediately reduce the AE, the IVIG should be stopped and treatment administered.

Conclusion

Further comparisons of available IVIG products can be found in Immune Globulins: Therapeutic, Pharmaceutical, Cost, and Administration Considerations.4 Because of the differing characteristics, certain products may not be well tolerated by or recommended for particular patient populations. Additionally, individual patient tolerability may differ between certain products. Therefore, much care and consideration needs to be taken when selecting a particular IVIG for a particular patient. When treating patients with IVIG therapy, an important component is patient education about the brand being used, the rate escalation, risk factors they may have, their tolerance of the product, and any AEs they may have experienced. Another important component is documentation in the patient’s medical record of the IVIG brand used, infusion rate, patient risk factors, tolerance, and documentation of the brand selected (Figure 9). A stepwise approach that considers all of the components listed in the figures and tables will help foster the safe use of IVIG and reduce the adverse reactions commonly associated with the infusion of these products.

References


Figure 9. Patient education and documentation steps.

AE, adverse event