CLINICAL PEARLS: Plasmapheresis and Intravenous Immunoglobulin

Caitlin R. Musgrave, PharmD, BCPS
PGY2 Solid Organ Transplant Resident
Medical University of South Carolina

Disclosure

I have nothing to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation.

Objectives

To describe the mechanisms of plasmapheresis and intravenous immunoglobulin (IVIG) in the treatment of immunologic disorders

To evaluate pharmacologic considerations in patients undergoing plasmapheresis

To identify dosing and administration recommendations for the use of IVIG

Plasmapheresis and Plasma Exchange

Plasmapheresis (PP)

- Extracorporeal blood purification procedure
- Plasma is separated from the cellular components of blood
- Discontinuous flow centrifugation
- Continuous flow centrifugation
- Plasma filtration
- Solutes in the plasma component are removed via filtration
- Plasma is returned to the patient after treatment

Plasma Exchange (PE)

- Same initial process as plasmapheresis
- Rather than returning the patient’s filtered plasma, the plasma is discarded
- To maintain oncotic pressure and plasma volume, the removed plasma is replenished with an equal volume of replacement solution
- Most commonly 5% albumin
- Same oncotic pressure as normal plasma
- Prevents hypotension, edema
- Leads to a transient decrease in clotting factors, transport proteins, complement, and antibodies
**Plasmapheresis**

**Therapeutic Benefits of PP/PE**
- Based upon:
  - Removal of soluble factor responsible for the illness
  - Removes toxins only from the blood compartment
  - Tissue stores remain unaffected
  - Re-equilibration will decrease plasma concentrations
  - Replacement of a deficient factor with plasma infusion
- Can remove protein- and lipid-bound toxins
- Most effective for highly plasma protein bound, low volume of distribution toxins

**Possible Indications for PP/PE**
- Removal of large-molecular-weight pathogens from the circulation
- Antibodies
- Immune complexes
- Thrombotic factors
- Endotoxins
- Drugs
  - Cholesterol-containing lipoproteins

**Solute Removal with PP/PE**
- Elimination is a passive process described with linear kinetics
- The amount of solute removed from the plasma is dependent on the volume of plasma exchange

<table>
<thead>
<tr>
<th>Plasma Volume Exchange</th>
<th>Percentage of Solutes Removed from Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>78%</td>
</tr>
</tbody>
</table>

* 1 plasma volume = 3 Liters for a 70 kg patient

**Potential Adverse Effects of PP/PE**
- Volume overload
- Bleeding or thrombosis
- Immunoglobulin depletion
- Hypocalcemia
- Hypotension
- Allergic reactions
- Infections

**Pharmacologic Considerations in Patients Undergoing PP/PE**

**Therapeutic Drug Monitoring**
- Drug levels drawn midpheresis or immediately following PP/PE will overestimate drug clearance
- Levels should be drawn prior to PP/PE to establish a baseline value
- Post-pheresis levels should be delayed for several hours to allow for reequilibration
- Measuring free drug concentrations may be helpful in patients undergoing PP/PE
- Differences in replacement fluid may affect protein binding and activity

**Drug Clearance and Redosing**
- Recall that PP/PE clears highly plasma protein bound, low volume of distribution toxins most efficiently
- Little data exists regarding specific drugs that may require redosing following PP
  - Tobramycin: 4-36% removed by PP, may require supplemental dose
  - Phenytion: 3-10% removed by PP, may require supplemental dose
- Consider dosing narrow therapeutic index drugs following plasmapheresis
Plasmapheresis

**Pharmacologic Considerations in Patients Undergoing PP/PE**

**ACE Inhibitors**
- Plasmapheresis causes accumulation of bradykinin
- Negatively charged extracorporeal surfaces may activate the prekallikrein-kinin cascade
- ACE inhibitors prolong the half-life of bradykinin
- Accumulation of bradykinin can mediate inflammatory responses, increase vasodilatation, and contract smooth muscle
- May lead to hypotension, flushing, and GI distress
- Recommended to hold ACE inhibitors for at least 24 hours prior to plasmapheresis

---

Intravenous Immunoglobulin

**Intravenous Immunoglobulin (IVIG)**
- Preparation of highly purified immunoglobulin collected from a large pool of healthy human plasma
- Donors are screened against HIV, hepatitis B and C, and other retroviruses
- Product is purified via pasteurization, nanofiltration, and washes with solvents and detergents
- Contains over 90% intact, biologically active IgG
- Trace amounts of IgA, IgM, CD4, CD8, and human leukocyte antigen molecules

---

**Components of IVIG**

<table>
<thead>
<tr>
<th>Component</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar</td>
<td>• Sorbitol, glucose, sucrose</td>
</tr>
<tr>
<td></td>
<td>• Added to prevent aggregate formation</td>
</tr>
<tr>
<td>Sodium</td>
<td>• Ranges from trace amounts to 0.9%</td>
</tr>
<tr>
<td>pH</td>
<td>• Optimal pH to prevent aggregation is 4.0 to 4.5</td>
</tr>
<tr>
<td></td>
<td>• Many products have a final pH of 6.0 to 7.0</td>
</tr>
</tbody>
</table>

---

**What are the Components of IVIG?**

<table>
<thead>
<tr>
<th>Component</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolality</td>
<td>• Determined by sodium content</td>
</tr>
<tr>
<td></td>
<td>• Hypersomolar solutions may cause fluid shifts</td>
</tr>
<tr>
<td>IgA content</td>
<td>• IgA deficient patients are at risk for anaphylaxis from products containing IgA</td>
</tr>
<tr>
<td>Isohemagglutinin antibodies</td>
<td>• MHL, self-limiting hemolysis may occur due to residual anti-A and anti-B blood group antibodies</td>
</tr>
</tbody>
</table>
Intravenous Immunoglobulin

**IVIG Product Differences**

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>Sodium Content</th>
<th>Sugar Content</th>
<th>Dmcol/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogam</td>
<td>5.5</td>
<td>1-1.5 mEq/50 mL</td>
<td>5% sucrose</td>
<td>&gt;200-222 mEq/kg</td>
</tr>
<tr>
<td>Carimune</td>
<td>6.4-6.8</td>
<td>0.9% saline</td>
<td>5% sucrose</td>
<td>6% 650 mEq/kg</td>
</tr>
<tr>
<td>Flebogamma 5%</td>
<td>5.5-5.7</td>
<td>&lt;3.2 mEq/L</td>
<td>5% sorbitol</td>
<td>240-370 mEq/L</td>
</tr>
<tr>
<td>Gammagard Liquid 10%</td>
<td>4.6-6.1</td>
<td>Not detectable</td>
<td>No sugar</td>
<td>250-300 mEq/kg</td>
</tr>
<tr>
<td>Gammagard 5% 10%</td>
<td>6.4-7.2</td>
<td>0%</td>
<td>2% glucose</td>
<td>5% 650 mEq/L, 10% 1250 mEq/L</td>
</tr>
<tr>
<td>Gamunex</td>
<td>4.0-4.5</td>
<td>Trace</td>
<td>No sugar</td>
<td>258 mEq/kg</td>
</tr>
<tr>
<td>Octagam 5%</td>
<td>5.1-6.0</td>
<td>0</td>
<td>10% maltose</td>
<td>310-380 mEq/kg</td>
</tr>
<tr>
<td>Privigen</td>
<td>4.6-5.0</td>
<td>≤ 0.05 mmol/L</td>
<td>No sugar</td>
<td>240-440 mEq/kg</td>
</tr>
</tbody>
</table>

**Therapeutic Benefits of IVIG**

- First recognized that immune sera could ameliorate toxin-mediated disease in the early 1900s
- Utilized for prophylaxis and treatment of infectious diseases
- Primary immune deficiencies described in the 1950s
- Utilizes for substitution of immunoglobulins
- During treatment of two children with hypogammaglobulinemia and coincidental idiopathic thrombocytopenic purpura, an increase in platelets was observed
- Immunomodulatory effects began to be postulated

**Potential Indications for IVIG**

<table>
<thead>
<tr>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunodeficiencies</strong> Primary, secondary (HIV)</td>
</tr>
<tr>
<td><strong>Autoimmune</strong> Systemic lupus erythematosus</td>
</tr>
<tr>
<td><strong>Dermatologic</strong> Pemphigus, pemphigoid, bullous dermatoses</td>
</tr>
<tr>
<td><strong>Infectious</strong> Sepsis; cytomegalovirus; bacterial infections in Ig deficiency</td>
</tr>
<tr>
<td><strong>Hematologic</strong> Sickle cell; hemolytic anemia; thrombocytopenias (ITP)</td>
</tr>
<tr>
<td><strong>Neurological</strong> Multiple sclerosis, myasthenia gravis, Guillain-Barre</td>
</tr>
<tr>
<td><strong>Transplantation</strong> GVHD after BMT; antibody mediated rejection after SOT</td>
</tr>
</tbody>
</table>

**Potential Adverse Effects of IVIG**

- Generally well-tolerated
- Most common adverse effects
  - Acute hypersensitivity
  - Due to IgG aggregation and complement activation
  - Premedicate with acetaminophen, diphenhydramine
  - Patients with IgA deficiencies have a higher risk of anaphylaxis
- Less common adverse effects
  - Thromboembolism
  - Renal failure
  - Hypotension
  - Fluid overload
Plasmapheresis

Pharmacologic Considerations in Patients Receiving IVIG

Dosing

- Differs based on indication
  - Replacement therapy in primary immunodeficiencies:
    - 400-500 mg/kg every 3-4 weeks
    - Achieves serum IgG levels 620-1400 mg/dL
  - Idiopathic thrombocytopenic purpura:
    - 400 mg/kg IV on 2 to 5 consecutive days or 1 gm/kg for 1 to 2 doses
  - Antibody mediated rejection in solid organ transplantation:
    - 100 mg/kg following each plasmapheresis session or 2 gm/kg following the last plasmapheresis session

PLASMAPHERESIS AND INTRAVENOUS IMMUNOGLOBULIN

Take Home Points

- Plasmapheresis and intravenous immunoglobulin are two treatment modalities which are being increasingly employed (both separately and in combination) for various immune deficiencies or for immunomodulation
- The hospital-based pharmacist has an important role to play in ensuring these therapies are used successfully and safely
  - Therapeutic drug monitoring in patients undergoing plasmapheresis
  - Holding ACE inhibitors prior to plasmapheresis
  - IVIG product selection
  - Premedicating prior to IVIG therapy
  - Appropriate weight-based dosing and dose rounding of IVIG

CLINICAL PEARLS: Plasmapheresis and Intravenous Immunoglobulin

Caitlin R. Musgrave, PharmD, BCPS
PGY2 Solid Organ Transplant Resident
Medical University of South Carolina