



DRUG ALERT

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INTRAVENOUS IMMUNOGLOBULIN (IVIG)

Introduction

Intravenous immunoglobulins (IVIGs) are sterile, purified immunoglobulin G (IgG) products manufactured from pooled human plasma from 3000 -10000 healthy blood donors. It typically contains more than 95% unmodified IgG and only trace amounts of immunoglobulin A (IgA) or immunoglobulin M (IgM). The entire array of variable (antigen-binding) regions of antibodies in normal serum is contained in IVIG.

IVIG is used to treat a variety of autoimmune, infectious, and idiopathic diseases. It is an approved treatment for graft versus host disease (GVHD) and idiopathic thrombocytopenic purpura (ITP). It is accepted for use in persons with Kawasaki disease, Guillain-Barre syndrome, and polymyositis/dermatomyositis.

Mechanism of action

IVIG is an immunomodulating agent that has multiple activities. Not all mechanisms play a role in each condition treated. Some of the proposed mechanisms are:

- ▶ Functional blockade of Fc receptors on splenic macrophages in ITP patients.
- ▶ Increase in solubility and clearance of immune complex in vasculitis patients.
- ▶ Neutralization of circulating autoantibodies (anti-idiotypic antibodies) in autoimmune disorders.
- ▶ Inhibition of complement mediated damage (decrease in C3b and membrane attack complex in target cells) plays role in dermatomyositis.
- ▶ Modulation of production of proinflammatory cytokines and prevention of deposition of membrane attack complexes on target surface is shown to be the mechanism in inflammatory conditions like Kawasaki disease.
- ▶ Neutralization of bacterial toxins and viruses might be involved in treatment of infections.

Pharmacokinetics

IgG appears in serum immediately and the serum concentration attained is directly related to the dose of IVIG administered. Following IV administration the

reported half-life is about 21 to 29 days. Interindividual variation in half-life is seen especially in patients with immunodeficiency. It is distributed to extravascular spaces and is eliminated through reticuloendothelial system.

Uses/ Indications

The US Food and Drug Administration (USFDA) approved indications for the use of IVIG are:

1. Primary immunodeficiencies
2. Immune-mediated thrombocytopenia
3. Kawasaki disease
4. Hematopoietic stem cell transplantation in patients older than 20 years.
5. Chronic B-cell lymphocytic leukemia
6. Pediatric HIV type 1 infection

There are many off-label uses for IVIG, in which controlled trials establishing the safety and efficacy are still needed. Some of these off-label uses are:

1. *Hematological diseases:* Aplastic anemia, pure red cell aplasia, diamond-blackfan anemia, autoimmune hemolytic anemia, hemolytic disease of the newborn, acquired factor VIII inhibitors, acquired von Willebrand disease, immune-mediated neutropenia and neonatal alloimmune/autoimmune thrombocytopenia.
2. *Infectious disease:* Acquired infectious disease that could be deleterious in low birth weight baby (ie, <1500 g), solid organ transplantation, extensive burns and HIV infection.
3. *Neurological diseases:* Guillain-Barré syndrome (most commonly used in India), chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy and multiple sclerosis.
4. *Rheumatological diseases:* Rheumatoid arthritis (adult and juvenile), systemic lupus erythematosus, systemic vasculitides, dermatomyositis, polymyositis, inclusion-body myositis and Wegeners granulomatosis.
5. *Respiratory disease:* Asthma.

6. *Miscellaneous*: Behcet syndrome, autoimmune blistering dermatoses, acute idiopathic dysautonomia, acute disseminated encephalomyelitis, hemophagocytic syndrome, multiple myeloma and POEMS syndrome.

Dosage

The recommended dose of IVIG is 400 mg/kg/day for 5 days (total dose 2gm/kg) in the form of an IV infusion. Recent trials in patients with ITP have found a dose of 1gm/kg/day for 2 days to be superior to the conventional dose.

It is necessary to monitor IVIG therapy. Careful history has to be obtained regarding hepatic or kidney disease or a history of reaction to blood products or transfusion reaction before administering IVIG.

Adverse effects:

Adverse reactions to IVIG have been reported in 10% or less of individuals receiving the drug and it is still less if the patient is not immunodeficient. Most adverse reactions to IVIG appear to be related to the rate of administration rather than the dose and may be relieved by decreasing the rate of administration.

The most frequent adverse effect reported in clinical trials occurring during or after infusion are headache, chills, fever and irritability. Others are myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension. If these are anticipated, premedication with antihistamines and intravenous hydrocortisone may alleviate these events. The other immediate reaction that can occur is infusion reaction like chills, fever, dizziness, nausea, vomiting, hypotension and clinical manifestations of anaphylaxis. These appear to be related to rate of infusion.

IVIG administration can induce serious anaphylactoid reactions in patients with IgA deficiency, immediately after iv administration (1 in 500-1000 patients). This is associated with sensitization to IgA in patients with IgA deficiency. It can be prevented by using IgA-depleted immune globulin.

Renal adverse effects like renal dysfunction, acute renal failure, osmotic nephrosis and death have been reported. Increase in serum creatinine and BUN can occur within 1-2 days of infusion. Preparations stabilized with sucrose are more likely to produce IVIG associated renal dysfunction.

Aseptic meningitis syndrome reported rarely is seen in patients receiving high doses or rapid infusion of IVIG. This is usually seen within hours to 2 days of infusion of immunoglobulin. Patients with migraine may be more susceptible to aseptic meningitis syndrome.

Other rare events reported with the use of IVIG are thrombotic effects, hemolysis (due to blood group antibodies) and noncardiogenic pulmonary edema.

Cost benefit aspect

IVIG is an expensive drug. Present cost of treatment in an individual weighing 60 kg is approximately Rs.1.20 lakh. In view of the potential life saving benefits, the cost effectiveness of IVIG outweighs the initial high expenditure when judiciously used in properly selected patients. Since the resources are limited and it may not be feasible to provide this drug to all patients suffering from immunological diseases, proper selection of patients based on cost benefit and cost effectiveness analysis becomes very important.

Experience at JIPMER

At JIPMER this drug has been used mainly for the treatment of Gullian-Barre Syndrome (18 patients) and ITP (2 patients). No significant adverse effects to IVIG infusion were noted and all the patients showed improvement in their clinical condition.

The management of GBS consists of both supportive and immunomodulatory treatments, of which intravenous immunoglobulin (IVIG) and plasma exchange (PE) are considered most effective. A number of randomized, controlled studies have shown IVIG to be at least as effective as PE in the treatment of GBS, and in some cases, superior. Moreover, IVIG has been found to be safer than PE, having a lower frequency of complications. IVIG has also been found to be effective and safe in the treatment of pediatric patients with GBS. Thus, its efficacy, safety, and availability make it the treatment of choice in many patients with GBS. However, its use should be limited only to the patients with significant disability of less than 2 weeks duration (ie. bed ridden, requiring support to walk, or on assisted ventilation).

IVIG has been found to be quite useful in patients with ITP in the setting of very low platelet counts to prevent major life threatening bleeds.

Key points

1. IVIG is an immunomodulating agent used to treat a variety of autoimmune, inflammatory, infectious, and idiopathic diseases particularly GBS and ITP in our setting.
2. IVIG contains natural antibodies, accounting for many of its immunomodulating effects.
3. Since IVIG is prepared from pooled plasma of healthy blood donors, life threatening anaphylactic reactions are unlikely to occur except in patients with IgA deficiency.

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