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Short Communication

Intravenous immunoglobulin in pediatrics: A review

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ABSTRACT

There has been a rapid expansion of the use of intravenous immunoglobulin (IVIG) for an ever-growing number of conditions. IVIG is used at a 'replacement dose' (400–600 mg/kg/month) in antibody deficiencies and is used at a high dose (2 g/kg) as an 'immunomodulatory' agent in an increasing number of immune and inflammatory disorders.[1] The limitations for IVIG are the cost of the preparation and the need for intravenous infusions. Due to the cost, shortages and growing use of IVIG there have been attempts to develop evidence-based guidelines for the use of IVIG in a wide variety of immune disorders in children and neonates. This commentary provides the recommendations and recent publication regarding the use of IVIG in various conditions in children.

Introduction

There has been a rapid expansion of the use of intravenous immunoglobulin (IVIG) for an ever-growing number of conditions in children and neonates.[1] IVIG has a few proven indications and many potential ones. It has had a major impact in the treatment of conditions in the fields of neurology, haematology, rheumatology and dermatology. It is safe and does not have the side-effects of steroids or other immunosuppressive agents. IVIG is used at a 'replacement dose' (400–600 mg/kg/month) in antibody deficiencies and is used at a high dose (2 g/kg) as an 'immunomodulatory' agent in an increasing number of immune and inflammatory disorders.[2] The limitations for IVIG are the cost of the preparation and the need for intravenous infusions. Due to the cost, shortages and growing use of IVIG there is a growing need to develop evidence-based guidelines for the use of IVIG in a wide variety of immune disorders in children and neonates. Here, we present a review of IVIG use in children, along with some of the common uses at our centre.

IVIG: its advent and importance

Immunoglobulin replacement has been standard therapy for patients with primary immune deficiency diseases since its use by Bruton in 1952.[3,4] For many years, these preparations could only be given intramuscularly. However injections were painful, the IgG was absorbed slowly and it was difficult to maintain IgG levels above 2 g/l. Although attempts were made to modify immune serum globulin for intravenous use, intramuscular use remained the sole form of replacement therapy until 1981 (29 years later) when intravenous preparations became commercially available. This reduced the pain

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of administration and allowed larger volumes to be infused. Today, over 25 IVIG preparations are available worldwide which have been approved by various regulatory bodies.[5] The various IVIG products differ in a number of ways including immunoglobulin and IgG subclass distribution, antibody content, approved maximum infusion rate and side-effects.[6] The characteristics of the various products may result in differences in efficacy and safety which may have a significant impact on the choice of product for some patients. Differences in the manufacturing processes of different IVIG preparations affect opsonic activity, Fc-receptor function and complement fixation.[5,6] An ideal IVIG preparation would contain structurally and functionally intact immunoglobulin molecules with a normal biological half-life and a normal proportion of IgG subclasses. The preparation should contain high levels of antibody or antibodies relevant to its proposed use. All IVIG preparations are isolated from pooled human plasma (1000–10,000 donors) by the Cohn alcohol fractionation method which results in five plasma fractions.[6] The Cohn fraction II contains the bulk of the antibodies for therapeutic use. This fraction is further purified for the production of IVIG. The WHO has established the following production criteria for IVIG (1982)[7]:

1. Each lot should be derived from plasma pooled from at least 1000 donors.
2. It should contain at least 90% intact IgG with the subclasses present in ratios similar to normal pooled plasma.
3. IgG molecules should maintain biological activity such as complement fixation.
4. It should be free from contaminants of prekallikrein activator kinins, plasma proteases and preservatives.
5. It should be free from infectious agents. As for all blood products donors are screened for hepatitis B surface antigen, HIV-p24 antigen, and antibodies to syphilis, HIV-1, HIV-2 and hepatitis C.

IVIG acts via a variety of mechanisms in different disease states. The mechanisms of action of therapeutic IVIG are complex. In many conditions advances in the understanding of its actions have been made. The predominant mechanisms depend on both the IVIG dose and on the pathogenesis of the underlying disease and can be divided into four broad groups[8]:

1. Actions mediated via the variable regions Fab.
2. Actions of Fc region on a range of receptors.
3. Actions mediated by complement binding within the Fc fragment.
4. Immunomodulatory substances other than antibody in the IVIG preparations.

When to use

IVIG's effect last between 2 weeks and 3 months. It is mainly used as treatment in three major categories[9]: (a) Immune deficiencies such as X-linked agammaglobulinemia, hypogammaglobulinemia (primary immune deficiencies), and acquired compromised immunity conditions (secondary immune deficiencies) featuring low antibody levels. (b) Autoimmune diseases, e.g. Immune thrombocytopaenia (ITP), and Inflammatory diseases, e.g. Kawasaki disease. (c) Acute infections.

IVIG is an infusion of IgG antibodies only. Therefore, peripheral tissues that are defended mainly by IgA antibodies, such as the eyes, lungs, gut and urinary tract are not fully protected by IVIG treatment. IVIG has many uses and is an important treatment in many diseases. The original use was as replacement therapy (400–600 mg/kg/month) in primary and secondary antibody deficiencies. However, IVIG has many immunomodulatory and anti-inflammatory effects at higher doses (2 g/kg/d) and now more than 100 inflammatory and autoimmune disorders are treated with IVIG.[9,10] IVIG therapy has a few proven indications and many potential ones. There are currently six clinical indications in the USA with Food and Drug Administration (FDA) approval[9]:

1. Treatment of primary immunodeficiencies.
2. Prevention of bacterial infections in patients with hypogammaglobulinaemia and recurrent infection caused by B-cell chronic lymphocytic leukaemia.
3. Prevention of coronary artery aneurysms in Kawasaki disease.
4. Prevention of infections, pneumonia and acute graft versus host disease (GVHD) after bone marrow transplantation.
5. Reduction of serious bacterial infection in children with HIV.
6. Increase of platelet count in idiopathic thrombocytopenic purpura to prevent or control bleeding.

There are many disorders for which IVIG is used as a treatment in children. Some of the common indications can be grouped as[9–14]:

a) Neurology – Guillain Barre syndrome, Chronic inflammatory demyelinating polyradiculopathy (CIDP), Dermatomyositis and inflammatory myopathies, Myasthenia gravis, rare childhood epilepsy (Lennox gastaut seizure, Landau kleffner seizure), Opsoclonus myoclonus ataxia, PANDAS (Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) – OCD, anxiety, depression, emotional lability.
b) Haematology – Idiopathic thrombocytopenic purpura, Pure red cell aplasia, Pure white cell aplasia, Immune neutropenia, Immune haemolytic anaemia.
c) Immunology – Primary antibody deficiencies (XLA, CVID, HIGM, WAS and others), Secondary antibody deficiencies.
d) Dermatology – Kawasaki syndrome, Dermatomyositis, Toxic epidermal necrolysis, Blistering diseases, Immune urticaria, Atopic dermatitis, Pyoderma gangrenosum.
e) Neonatology – Haemolytic disease of newborn due to Rh and ABO incompatibility, Neonatal alloimmune thrombocytopenic purpura, Bacterial sepsis in preterms.
f) Others – Myocarditis, Systemic lupus erythematosus, Streptococcal toxic shock syndrome, Autoimmune uveitis.

IVIG dose

The usual dose of IVIG for antibody replacement is between 400 and 600 mg/kg of body weight every 2–4 weeks. The dose