Editorial

Clinical usage of intravenous immunoglobulin in children

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There are currently only six clinical indications for intravenous immunoglobulin (IVIG) approved by the Food and Drug Administration (FDA) of the United States of America[1]:

1. Treatment of primary immune-deficiencies.
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 thrombocytopaenic purpura to prevent or control bleeding.

However, there are many conditions for which IVIG is used in children, not all of which are approved by the FDA. These indications are as follows:[1-6]

- Neurology: Guillain-Barre syndrome, chronic inflammatory demyelinating polyradiculopathy, inflammatory myopathies, myasthenia gravis, rare childhood epilepsy (Lennox-Gastaut seizure, Landau-Kleffner seizure), opsoclonus-myoclonus ataxia, paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, obsessive compulsive disorder
- Haematology: Idiopathic thrombocytopenic purpura, pure red cell aplasia, pure white cell aplasia, immune neutropenia, immune haemolytic anaemia.
- Immunology: Primary and secondary antibody deficiencies.
- Dermatology: Kawasaki syndrome, dermatomyositis, toxic epidermal necrolysis, blistering diseases, immune urticaria, atopic dermatitis, pyoderma gangrenosum.
- Neonatology: Haemolytic disease of newborn due to Rh and ABO incompatibility, neonatal alloimmune thrombocytopenic purpura, bacterial sepsis in preterms.
- Others: Myocarditis, systemic lupus erythematosus, streptococcal toxic shock syndrome, autoimmune uveitis.

The usual dose of IVIG for antibody replacement is between 400 and 600 mg/kg of body weight every 2–4 weeks. The dose is adjusted so that the trough level just before the next infusion is at least 500 mg/dl. For other uses the doses range between 400 mg/kg/day for 5 days or a more rapid course of 1–2 g/kg given over 1–2 days[7]. 'High dose' IVIG was first used in immune thrombocytopenic purpura (ITP) in children[8].

Currently, several IVIG preparations are available worldwide approved by various regulatory bodies[9]. These IVIG products differ in several ways including immunoglobulin and IgG subclass distribution, antibody content, approved maximum infusion rate and side-effects[10]. Differences in the manufacturing processes of different IVIG preparations affect opsonic activity, Fc-receptor function and complement fixation[9,10]. The WHO has established the following production criteria for IVIG (1982):[11]

- Each lot should be derived from plasma pooled from at least 1000 donors.
- It should contain at least 90% intact IgG with the subclasses present in ratios similar to normal pooled plasma.
- IgG molecules should maintain biological activity such as complement fixation.
- It should be free from contaminants of prekallikrein activator kinins, plasma proteases and preservatives.
- 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 through several mechanisms in different disease states. The predominant mechanisms depend on both the IVIG dose and on the pathogenesis of the underlying disease and fall into four broad groups:[12]

- Actions mediated via the variable regions Fab.
- Actions of Fc region on a range of receptors.

- Actions mediated by complement binding within the Fc fragment.
- Immunomodulatory substances other than antibody in the IVIG preparations.

Systemic reactions to IVIG infusion range from 3% to 15%[13]. They are usually self-limiting and can be avoided by decreasing the rate of infusion. Infusion rates are usually started at 0.01–0.02 ml/kg/min and increased up to 0.1 ml/kg/min. Most IVIG reactions are mild and non-anaphylactoid and include backache, abdominal pain, nausea, chills, rhinitis, low-grade fever, myalgia and headaches. More serious adverse events can occur during or soon after infusion and include anaphylaxis, renal, cardiovascular, central nervous system and haematological events[14].

Because of the cost, shortages as well as availability issues, and increasing use of IVIG, many countries have attempted to develop guidelines for use of IVIG[13,15]. Clinicians should prescribe IVIG only in conditions where efficacy is supported by evidence-based studies. Some firm indications for IVIG use in children are as follows[7]:-

- Primary immunodeficiency states.
- Kawasaki disease.
- Idiopathic thrombocytopenic purpura.
- Guillain-Barre syndrome
- Reduction of serious bacterial infection in children with HIV.
- Bacterial sepsis in preterms.

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The author declares that there are no conflicts of interest