

Adverse Reactions to Intravenous Immunoglobulins - Our Experience

Lidija Kareva*, Kristina Mironska, Katerina Stavric, Arjeta Hasani

University Pediatric Hospital, Ss Cyril and Methodius University of Skopje, Skopje, Republic Macedonia

Abstract

Citation: Kareva L, Mironska K, Stavric K, Hasani A. Adverse Reactions to Intravenous Immunoglobulins-Our Experience. Open Access Maced J Med Sci. <https://doi.org/10.3889/oamjms.2018.513>

Keywords: Intravenous immunoglobulins; adverse reactions

***Correspondence:** Lidija Kareva, Department of Immunology, University Pediatric Hospital, Ss Cyril and Methodius University of Skopje, Skopje, Republic Macedonia. E-mail: kvlidija@yahoo.com

Received: 09-Nov-2018; **Revised:** 04-Dec-2018; **Accepted:** 05-Dec-2018; **Online first:** 17-Dec-2018

Copyright: © 2018 Lidija Kareva, Kristina Mironska, Katerina Stavric, Arjeta Hasani. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

BACKGROUND: Adverse reactions to intravenous immunoglobulins (IVIG) are divided by organ system involved, or by timing of onset—immediate which occur during infusion usually rate-related, true IgE-mediated anaphylaxis and delayed reaction which occur hours to days after the infusion.

AIM: To describe the adverse events of patients given IVIG infusions.

METHODS: Total number of patients receiving IVIG was 41 with 25 males (60.97%) and 16 females (39.02%), age 2 months-35 years. A total number of infusions was 1350.

RESULTS: Total number of adverse reactions 15, 14 patients with immediate-type and 1 with delayed type. Total percentage of adverse reactions in a given sample was 1.1% of all IVIG infusions. Fever was the most common immediate type of reaction occurring in 11 patients (78.57%) followed by acrocyanosis 10 patients (71.42%), skin rash 9 patients (64.28%) and headache 8 patients (57.14). Delayed-type of reactions (like fever, headache and vomiting) was present in one patient. Majority of the adverse effects occurred at the infusion rate higher than 1, 5 ml/kg/hour, which is still within recommended speed.

CONCLUSION: About 1.1% of IVG infusions were with adverse events. Most common manifestations were: fever, acrocyanosis, skin rash and headache, which occurred 1-6 hours from the beginning of the infusion. The occurrence of adverse reactions to IVIG was related to the infusion rates in a fashion that faster infusion rate gives more reactions. Adverse reactions were managed by reduction of the infusion rate and administration of medications such as paracetamol, antihistamines and steroids.

Introduction

Intravenous immunoglobulins (IVIG) are the preparation of highly purified IgG derived from large pools of human plasma via ethanol fractionation. Preparations are stabilised using substances such as human albumin, glycine, polyethene glycol, or sugars such as sucrose, maltose or glucose. Intravenous immunoglobulins are mainly used as replacement therapy for immunodeficiency, and immunomodulatory therapy in autoimmune and inflammatory conditions [1], [2], [3]. These preparations are manufactured by different companies and are at the disposal of the

clinician. As a result of preparation processes reactions may occur to either the immunoglobulin, aggregates the preparation or the stabilising agent [5].

Possible adverse effects of IVIG may be divided by organ system or by timing of onset, i.e., immediate or delayed. Immediate reactions occur during the infusion, and include rate-related reactions, true immunoglobulin E (IgE)-mediated anaphylaxis (in immunoglobulin A (IgA)-deficient patients), and reactions related to concurrent infection [4], [7], [8], [9], [10], [11], [12]. Delayed reactions generally occur hours to days after the infusion [13]. These can be a headache, aseptic meningitis, acute kidney injury, hemolysis, venous thrombosis, myocardial infarction,

transient ischemic attacks, and stroke. Some of these, particularly thrombotic events, may also occur during infusions [14]. These adverse events may be due to the relative "impurity" of the commercial preparations, or the undesirable effects of its active component immunoglobulin G (IgG). The most common adverse effects occur soon after infusions and can include a headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension [4], [7], [8], [9], [10], [11], [12]. Intravenous immunoglobulin is a biological product, and potentially important product-manufacturing differences may exist. It is perhaps for this reason that adverse effects appear to vary considerably among different IVIG preparations available in the market [5], [6].

This study aims to determine the incidence and type of adverse events following the infusion of different IVIG preparations. Understanding the common side effects and the IVIG preparations are important in caring for patients receiving IVIG.

Methods

This is a retrospective study. Records of patients given IVIG at the ward and the outpatient department from January 2006 to January 2016 at Immunology department of Pediatric Hospital-Skopje were reviewed. Demographic data such as age, sex, indication for IVIG treatment were taken from the charts of the patients. Total of 41 patients receives IVIG preparations, 25 males (60.97%), 16 females (39.02%), age 2 months -35 years, with a total number of infusions 1350. Indication for IVIG treatment and dosage where as follows: 18 patients with primary immunodeficiency 400 mg/kg/monthly, 5 patients with Kawasaki syndrome 400 mg/kg/5doses/daily, 10 patients with sepsis 400 mg/kg/dose/1-2 times divided by 2 days, 3 patients with atopic dermatitis and transient infantile hypogammaglobulinemia 400 mg/kg/monthly/6months, 2 patients with transient infantile hypogammaglobulinemia and recurrent infections 400 mg/kg/monthly/6months and 5 patients with ITP 400 mg/kg/5doses/daily. The rate of IVIG infusions was 0.5 ml/kg/hour and increased every 15-30 min, based on the patient's tolerance up to 3 ml/kg/hour. IVIG preparation used was Kiovig- Baxter (glycin as a stabiliser) IgVena-Kedrion (sucrose as a stabiliser) Octagam-Octapharma (maltose as a stabiliser).

Once patients with adverse reactions have been identified, the following data were taken and reviewed: a specific type of adverse reaction to IVIG; the time interval between onset of adverse reaction and beginning of IVIG infusion and appearance of adverse reactions; IVIG preparation, dose and infusion rate; and medical management did during the

adverse event. Statistics were used to analyse and interpret the data.

Results

A total number of patients receiving IVIG was 41 [25 males (60.97%), 16 females (39.02)] with age 2 months to 35 years. A total number of infusions was 1350. Total numbers of adverse reactions were 15, 14 patients with immediate-type and 1 with delayed type. Total percentage of adverse reactions in a given sample was 1.1% of all IVIG infusions. Immediate-type of reactions were: Fever was the most common immediate type of reaction occurring in 11 patients (78.57%) followed by acrocyanosis 10 (71.42%) and skin rash 9 (64.28%), followed by headache 8 (57.14%) shortness of breath 6 (42.85%), perioral cyanosis 6 (42.85), hypotension 5 (35.71) and chest pain 3 (21.42%), (Table 1).

Table1: Immediate adverse reactions to IVIG

Symptoms	Number of patients (%)
Fever	11 (78.57)
Acrocyanosis	10 (71.42)
Skin rash	9 (64.28)
A headache	8 (57.14)
Perioral cyanosis	6 (42.82)
Shortness of breath	6 (42.82)
Hypotension	5 (35.71)
Chest pain	3 (21.42)

Delayed types of reaction were a headache, fever and vomiting in one patient (6.6%), (Table 2).

Table 2: Delayed adverse reactions to IVIG

Symptoms	No of patients
Vomiting	1
Fever	1
A headache	1

Time of onset from the beginning of the infusion: 0-30 min 7 patients, 30 min to 1 hour 5 patients, 1 hour to 6 hours 2 patients, 24 hours 1 patient, (Table 3).

Table 3: IVIG infusions and time of onset of adverse reactions

Time from the beginning of the infusion	Frequency
0-30 min	7
30-60 min	5
60 min- 6hours	2
24 hours	1

Symptoms were affected by fast infusion rates, the faster the infusion rate, the more adverse reactions occur. In our study, most of the adverse effects occurred at the infusion rate higher than 1, 5 ml/kg/hour, which is still within the recommended speed. There was notable difference in frequency of adverse reactions depending on the brand of IVIG used for infusion (Figure 1).

Reactions were managed by reducing the

rate of infusion and giving of medications such as paracetamol, antihistamines and steroids.

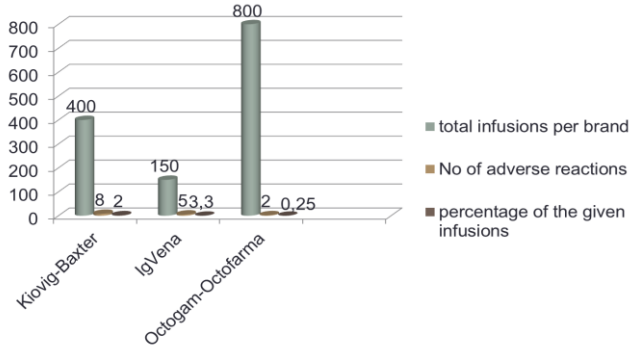


Figure 1: Adverse reactions of IVIG per brand

Discussion

The pathogenesis of adverse reactions of IVIG is still unknown. IVIG preparations differ in their composition and properties, and these can contribute to its efficacy and tolerability [5], [6]. Major determinants are immunoglobulins, particularly IgA content, sodium content, sugar content and osmolality [6]. The most common adverse reactions of IVIG in our study are the immediate type, occur in the first 30-60 min of administration. This includes fever, chills, headache, skin rash and even some vasomotor and cardiovascular manifestations marked by changes in blood pressure, tachycardia and cyanosis. These reactions are most common [4], [7], [8], [9], [10], [11], [12] and probably are results from aggregated immunoglobulin molecules which cause the complement system to be activated, antigen-antibody reactions, possible contaminants or even stabilizers that may have been used during the manufacturing process. Symptoms were affected by fast infusion rates, faster the infusion rate more adverse reactions occur. In our study, most of the adverse effects occurred at the infusion rate higher than 1, 5 ml/kg/hour, which is still within the recommended speed. Delayed types of reaction were a headache, fever and vomiting in one patient. This finding is not in correlation with the finding of other authors [13], where the majority of the reaction were delayed type.

Sugars such as sorbitol, maltose, sucrose and glucose are added to some IVIG preparations as stabilisers which will prevent aggregate formation. However, there seems to be an association between these sugars and the development of acute renal failure or renal insufficiency in treated patients [6]. Sugar-stabilised solutions, such as IgVena and Octagam tend to have higher osmolality compared to the sugar-free preparations like Kiovig which is glycine stabilised. The hyperosmolar solutions may cause

fluid shifts when given intravenously, and this may result in hemodynamic changes leading to infusion-related adverse effects [6]. The sodium content of IVIG determines the osmolality of the infused solution, which in turn can affect tolerability and occurrence of adverse effects. Patients with hypertension and renal impairment may be affected by a high-sodium content solution. The IgA content of a solution is significant for patients with IgA deficiency. These patients are more likely to develop severe and sometimes fatal anaphylactic reactions [1]. The content of IgA varies among different IVIG preparations. However, using a preparation that is low in IgA does not guarantee an adverse reaction-free infusion. In our study, we were not able to determine reactions due to anti-IgA antibodies present in the patients because we don't have laboratory tests for anti-IgA antibodies.

These adverse reactions can be managed by slowing down the infusion rate and giving of medications such as antihistamines, paracetamol and corticosteroids, or switching the IVIG to different preparation.

In conclusion, the ability to tolerate the effects of IVIG infusion without experiencing adverse effects varies from one person to another and from one IVIG preparation to another. The rate of infusion influences the occurrence of adverse reactions, as well as osmolality, sugar and IgA content of a preparation. In our study, 1.1% of patients given IVIG infusions experienced adverse events, which is less than the percentage of the reactions described in the literature. We speculate that the low rate of infusion which is preferable at our clinic is the main reason for less occurrence of adverse reactions, as well as the type of the immunoglobulins we used. In our study, most of the adverse effects occurred at the higher infusion rate of the IVIG preparation, but still in the recommended speed from the manufacturer. IVIG preparations differ in their composition and properties, and these can contribute to its efficacy and tolerability with some types showing a greater rate of adverse reactions than the others. Fever was the most common manifestation, followed by skin rash and chills. Symptoms occurred within 1 to 6 h from onset of infusion, were affected by fast infusion rates, and managed by reducing the rate of infusion and giving of medications such as paracetamol, antihistamines and steroids.

References

1. Provan D, Nokes TJ, Agrawal S. IVIG Guideline Development Group of the IVIg Expert Working Group Clinical Guidelines for Immunoglobulin Use. 2008.
2. Kareva L. Intravenous immunoglobulin therapy in medical praxis. Journal of IMAB: Annual Proceeding (Scientific Papers). 2016; 22(4):1403-6. <https://doi.org/10.5272/jimab.2016224.1403>

3. Ballou M. The IgG molecule as a biological immune response modifier: mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory disorders. *J Allergy Clin Immunol*. 2011; 127:315–323. <https://doi.org/10.1016/j.jaci.2010.10.030> PMID:21185071
4. Singh-Grewal D, Kemp A, Wong M. A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. *Arch Dis Child*. 2006; 91:651–654. <https://doi.org/10.1136/adc.2005.078733> PMID:16638785 PMCid:PMC2083046
5. Purisima BC, Garcia RD, Leus A. A retrospective study on the efficacy of Gammagard S/D IVIG versus Vizcarra IVIG in the treatment of Kawasaki disease in Makati Medical Center from 1998-2003. *Philippine J Pediatr*. 2009; 57:11–16.
6. Lemm G. Composition and properties of IVIg preparations that affect tolerability and therapeutic efficacy. *Neurology*. 2002; 59:S28–S32. https://doi.org/10.1212/WNL.59.12_suppl_6.S28 PMID:12499468
7. Dashti-Khavidaki S, Aghamohammadi A, Farshadi F, Movahedi M, Parvaneh N, Pouladi N, Moazzami K, Cheraghi T, Mahdavian SA, Saghafi S, Heydari G, Abdollahzade S, Rezaei N. Adverse reactions of prophylactic intravenous immunoglobulin; a 13-year experience with 3004 infusions in Iranian patients with primary immunodeficiency diseases. *J Investig Allergol Clin Immunol*. 2009; 19:139–145. PMID:19476018
8. Kaba S, Keskindemirci G, Aydogmus C, Siraneci R, Erol FC. Immediate adverse reactions to intravenous immunoglobulin in children: a single center experience. *European annals of allergy and clinical immunology*. 2017; 49(1):11-4. PMID:28120600
9. Charhon N, Bonnet A, Schmitt Z, Charpiat B. A case of circulatory collapse during intravenous immunoglobulin therapy: A manageable adverse effect!. *Anaesthesia, critical care & pain medicine*. 2015; 34(2):113. <https://doi.org/10.1016/j.accpm.2014.08.004> PMID:25858620
10. Bichuetti-Silva DC, Furlan FP, Nobre FA, Pereira CT, Gonçalves TR, Gouveia-Pereira M, Rota R, Tavares L, Mazzucchelli JT, Costa-Carvalho BT. Immediate infusion-related adverse reactions to intravenous immunoglobulin in a prospective cohort of 1765 infusions. *International immunopharmacology*. 2014; 23(2):442-6. <https://doi.org/10.1016/j.intimp.2014.09.015> PMID:25257732
11. Rodríguez-Mireles KA, Galguera-Sauceda A, Gaspar-López A, López-Rocha EG, Campos-Romero F, del Rivero-Hernández L, Amaya-Mejía A, Galindo-Pacheco L, O'Farril-Romanillos P, Segura-Méndez NH. Adverse effects with ambulatory intravenous immunoglobulin administration in adult patients with common variable immunodeficiency. *Revista Alergia México*. 2014; 61(3):131-40. PMID:25177848
12. Palabrica FR, Kwong SL, Padua FR. Adverse events of intravenous immunoglobulin infusions: a ten-year retrospective study. *Asia Pacific Allergy*. 2013; 3(4):249-56. <https://doi.org/10.5415/apallergy.2013.3.4.249> PMID:24260730 PMCid:PMC3826603
13. Singh-Grewal D, Kemp A, Wong M. A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. *Archives of disease in childhood*. 2006; 91(8):651-4. <https://doi.org/10.1136/adc.2005.078733> PMID:16638785 PMCid:PMC2083046
14. Hefer D, Jaloudi M. Thromboembolic events as an emerging adverse effect during high-dose intravenous immunoglobulin therapy in elderly patients: a case report and discussion of the relevant literature. *Annals of hematology*. 2004; 83(10):661-5. <https://doi.org/10.1007/s00277-004-0895-2> PMID:15309520