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Case Report

Hemolytic Anemia After Administration of Intravenous Immunoglobulin in A Child Treated for Kawasaki Disease: An Under-Recognized Adverse Effect with Recognizable Risk Factors

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Abstract

Background: Haemolytic anaemia is a rare adverse effect of high dose intravenous immunoglobulin administration, described mainly in adults. Few cases have been recorded in children. A large percentage of them were treated for Kawasaki disease.

Case history: We describe here the case of a 9-month-old infant with Kawasaki disease who received 2 doses of intravenous immunoglobulin on days 9 and 11 of illness. Three days later he developed anaemia (drop of haemoglobin from 9,4 g/dL on admission to 6,6 g/dL on day 14), with a positive direct antiglobulin test (DAT). He received transfusion with packed red blood cells and his haemoglobin remained stable thereafter. The patient was blood group A+. The DAT demonstrated the presence of IgG but not complement on the surface of red blood cells. Unfortunately, no elution was performed in order to identify the antibodies responsible for the agglutination.

Conclusion: Due to the potential risk of haemolysis following IVIG administration, a haemoglobin counts 24-48 hours after infusion might be advisable. Further research is needed in order to identify the pathophysiological mechanisms of haemolysis after IVIG infusion and to provided safer IVIG products for patients at higher risk for this adverse effect.

Keywords: Kawasaki disease; intravenous immunoglobulin; haemolysis; anaemia; adverse effects

Introduction

Kawasaki disease is an acute systemic vasculitis of childhood of yet unknown ethology. It predominantly affects the medium sized arteries with a predilection for the coronary arteries. Complications include coronary artery aneurysms, pericarditis, myocarditis, mitral valve regurgitation and diminished left ventricular systolic function. It is currently the leading cause of acquired heart disease in childhood. Treatment guidelines for management of Kawasaki disease include high doses of intravenous immunoglobulin (IVIG) 2g/kg and aspirin. IVIG significantly lowers the incidence of coronary artery aneurysms. Nevertheless, in approximately 10-20% of patients fever persists ≥36 hours after the infusion. These patients are usually retreated with a second dose of IVIG 2g/kg, although other treatment options, such as methylprednisolone, anti-TNF and anti-interleukin agents exist [1]. IVIG is a pooled

plasma product that derives from thousands of volunteer donors. It is used as replacement therapy in primary and acquired humeral deficiencies or as an immunomodulatory agent in an increasing number of autoimmune and inflammatory disorders. It is generally well tolerated and serious adverse effects are relatively rare [2]. An under-recognized adverse effect of large doses of IVIG is hemolysis. It is a well-documented complication in adults, but few cases have been, thus far, reported in children. Berg et al recently published data from the pharmacovigilance databases of four manufacturing companies over a ten-year period (2002-2013). They identified 44 cases of hemolysis after IVIG administration in patients under the age of 18. 39% of them (17/44) were treated for Kawasaki disease which could imply that this patient group might be at higher risk [3]. Similarly, Luban et al identified, in published literature thus far, 15 cases of hemolysis after IVIG administration in children treated for Kawasaki disease [4].

Case Report

A 9-month-old boy presented with a 9day history of fever, maculopapular rash of the trunk with perineal desquamation, conjunctival injection and erythema of the oral mucosa with cracked lips and strawberry tongue. The clinical characteristics were diagnostic of Kawasaki disease. Laboratory findings on admission showed a haemoglobin of 9,4 g/dL, haematocrit 29,7%, white blood cells 15.2 x 109/L, platelets 573 x 109/L, C-reactive protein 34 mg/L, ESR 98 mm/hr. Mild dilation of the left coronary artery was noted on cardiologic evaluation. The patient received a dose of IVIG (2g/kg, Pregiven) on admission. A second dose of 2g/kg IVIG was administered on day 11 of illness, due to persistence of fever. Three days later pallor and tachycardia were noted. A full blood count on day 14 of illness revealed a drop in haemoglobin and haematocrit to 6,6 g/dL and 19,7% respectively. Peripheral blood smear showed the presence of spherocytes and the direct antiglobulin test (DAT) was positive for the presence of IgG but not complement on the surface of erythrocytes. Patient's blood group was A+. The infant received transfusion with packed red blood cells with a rise in haemoglobin. No further transfusion was needed. On the 18th and 19th day of illness, fever recurred. Laboratory findings were WBC 12.4 x 109/L, PLT 518 x 109/L, CRP 0,6 mg/dL and ESR 110 mm/hr and the patient was treated with 30 mg/kg methylprednisolone followed by per os prednisone. He remained afebrile thereafter, ESR decreased to 32mm/hr on day 26 and the patient was discharged on day 27 of illness. Cardiologic evaluation on discharge was normal. Laboratory findings and cardiologic evaluations during follow up were impeccable.

Discussion

Our patient experienced hemolysis following administration of large doses of IVIG. This case report adds to the small numbers of similar cases reported in children treated for Kawasaki disease. In patients with a positive DAT and evidence of hemolysis after IVIG administration, the antibodies on the red blood cells' surface after elution, are usually identified as anti-A and/or anti-B antibodies. Therefore, the presumed mechanism of hemolysis following IVIG administration is the presence of anti-A and anti-B antibodies in the IVIG preparations, deriving from the donors. These interact with the recipient's red blood cells, according to their blood group, causing agglutination and hemolysis. For this reason, the European Pharmacopoeia has specified that the maximum titter of anti-A and anti-B hemagglutinins in every lot of IVIG should be less than 1/64 [2]. Nonetheless hemolysis has been recorded even at titters as low as 1/16 or 1/8, implying that other factors may also play a role in the agglutination in vivo [3]. Another presumed mechanism is the presence in IVIG preparations of high molecular weight IgG complexes which can mimic immune complexes, causing erythrocyte sequestration. This mechanism does not depend on the presence of hemagglutinins and may explain the rare cases of hemolysis in blood group of patients. Risk factors for hemolysis following IVIG administration include large doses of IVIG (at least 2g/kg body weight), non-O blood group, pre-existing anaemia and concomitant inflammation [5]. As Kawasaki disease is an autoimmune disorder and anaemia is a common finding, this could explain why patients with Kawasaki disease seem to me more prone to haemolytic events following IVIG administration [3]. Other factors that may interfere with the risk for hemolysis are the titter of the hemagglutinins in the IVIG preparation, the strength of the patient's antigen expression and the affinity of the antibody for the antigen [5]. In conclusion, clinicians should bear in mind that hemolysis is a possible complication of IVIG administration. A measurement of haemoglobin 24-48 hours after completion of IVIG infusion might be recommended, especially for children with Kawasaki disease who need retreatment with a second dose of IVIG 2g/kg [4,5]. In case of a decrease in haemoglobin with a positive DAT, an elution could be performed in order to identify the hemagglutinins responsible. Measuring anti-A and anti-B titters in the administered lot might also be useful for research purposes. It yet remains unclear whether pharmaceutical properties of the drug, such the presence of aggregates or purity level, may influence the risk of hemolysis. Further evidence are needed in order to decide whether certain patients with Kawasaki disease might profit from the administration of selected, low-titter anti-A and anti-B, preparations [4].

Conflict of Interest

No conflict of interest.

Acknowledgement

The authors have nothing to disclose.

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