Intravenous Immunoglobulin Infusion Reactions in Kawasaki Disease Patients Who Undergo Sedation

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OBJECTIVES Although IVIG infusions are usually well tolerated, reactions can include hypotension, chills, and, rarely, anaphylactic reactions. Risk of adverse reactions correlates with dose and rate of IVIG infusion. An echocardiogram is the preferred imaging modality to detect coronary artery changes in acute Kawasaki disease (KD), but the quality of the study can be compromised if a child moves much during the imaging procedure. Thus, sedation is often required for children younger than 3 years of age. There is concern regarding coadministration of IVIG and sedatives. Therefore, the purpose of this analysis is to determine when the majority of IVIG infusion reactions occur to help find the optimal time to safely perform a sedated echocardiogram in patients with KD.

METHODS This is a retrospective, single-center analysis of patients with KD administered IVIG at Rady Children's Hospital San Diego from November 1, 2013, to October 31, 2016.

RESULTS Of the 260 subjects in this study, 34 (13%) had an IVIG infusion reaction consisting of either chills or hypotension. There were no anaphylactic reactions. All infusion reactions occurred within 4 hours of starting IVIG. No hypotension reactions occurred after 4 hours. All subjects were able to complete their IVIG infusion without any further complications.

CONCLUSIONS Given that the maximum IVIG infusion rate is reached at 1.5 hours per our hospital's policy and that the overwhelming majority of infusion reactions occurred within the first 4 hours, we found it is safe to coadminister IVIG with sedation 4 hours after initiation of IVIG infusion.

ABBREVIATIONS AHA, American Heart Association; IQR, interquartile range; IVIG, intravenous immunoglobulin; KD, Kawasaki disease

KEYWORDS adverse drug reaction; echocardiogram; infusion reactions; intravenous immunoglobulin; Kawasaki disease; pediatrics

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Introduction

Kawasaki disease (KD) is a systemic vasculitis that is the most common cause of acquired heart disease in children.¹ Early treatment with IVIG reduces the risk of coronary artery aneurysms from 25% to 5%.² Most IVIG infusions are well tolerated. However, up to 2.2% of patients can have an immediate IVIG infusion reaction during administration, which can include hypotension, tachycardia, nausea, vomiting, diarrhea, fever, chills, fatigue, and anaphylactic reactions.^{3,4} Although the most common side effects are fever and rash, these are common signs of KD and do not generally worsen in severity during IVIG administration. In fact, given the mechanism of action of IVIG in KD, fever and rash both improve with IVIG.⁵ Thus, we focused on the 2 next most common adverse reactions to IVIG, chills and hypotension, as this makes up approximately 25% of IVIG adverse reactions.⁶

Echocardiograms have a seminal role in the evaluation

of children with KD. A detailed echocardiogram is the imaging modality of choice to evaluate for the coronary artery abnormalities associated with KD, but it is difficult to obtain the level of detail required when a child has movement during the imaging procedure.⁶ It is especially difficult to get detailed imaging in this patient population as they are often febrile and irritable. Thus, sedation is often required for children younger than 3 years old. Margossian et al⁶ found that sedation was associated with improved visualization of the coronary arteries.

Concern has been raised about coadministration of IVIG and sedation primarily due to the potential risk for hypotension associated with IVIG, which could then be exacerbated with sedation medications. The purpose of this analysis is to find the optimal time to safely perform sedated echocardiograms in patients with KD receiving IVIG. We report our experience with the timing of IVIG infusion reactions in patients with KD to determine when the majority of IVIG infusion reactions occur.

Materials and Methods

This is a retrospective, single-center analysis of patients who met American Heart Association (AHA) criteria for KD and were treated with IVIG at Rady Children's Hospital San Diego between November 1, 2013, and October 31, 2016. All patients within the study dates who met AHA criteria for KD and received IVIG at our hospital were included in our study. No patients meeting this KD criteria were excluded from analysis. Clinical data, including demographics, vital signs (including BP), IVIG and sedation dosing regimens, IVIG reactions during IVIG administration as well as throughout the duration of hospitalization, and medications administered as a consequence of IVIG infusion reaction, were reported. We recognize IVIG has several different product formulations and our hospital uses Gammagard (Shire, Lexington, MA). IVIG for KD was administered following our hospital policy with a dose of 2 g/kg that is slowly ramped up with the maximum infusion rate reached at 1.5 hours. An IVIG infusion reaction was defined as chills, hypotension (systolic BP less than the fifth percentile for age), or anaphylaxis.⁷ We chose not to analyze other known immediate IVIG infusion reactions, such as fever, as this is also a sequelae of KD, and in fact IVIG administration reduces fever quickly in patients with KD. If an infusion reaction occurred, interventions included slowing or temporary discontinuation of the infusion (per provider's clinical judgement), as well as symptomatic therapy with a normal saline bolus, diphenhydramine, and/or acetaminophen. Once the adverse effect subsided and symptomatic therapy was completed, usually within 30 to 60 minutes of stopping the infusion, the IVIG was restarted at ½ of the rate at which the adverse effect occurred, and the rate was increased as per hospital guidelines. Details of the IVIG infusion reactions as well as medications administered in response to an IVIG infusion reaction or interruption of the IVIG infusion were recorded. Per our hospital clinical practice, an echocardiogram in children with acute KD should be done as soon as possible as medical decisions, including the need for initial IVIG therapy, additional anti-inflammatory therapy or anticoagulation, need to be made quickly in this disease.

Descriptive statistics, including medians and IQRs, for continuous variables such as patient age and time of sedation were used to describe patient characteristics and clinical outcomes. The median was used as the measure of central tendency, as the data were not normally distributed.

Results

In this study, 260 subjects were diagnosed with KD and treated with IVIG. Demographics and baseline clinical characteristics are listed in the Table. Of the 260 KD subjects, 202 (77.7%) were diagnosed with complete KD as per 2017 AHA requirement.¹ The remaining 58

Table. Patient Demographics (N = 260)

Characteristic	Result
Age, yr, median (IQR)	2.8 (1.5–4.9)
Males, n (%)	160 (61.5)
Days of illness,* median (IQR)	6.8 (5–7)
Race, n (%)	
Caucasian	60 (23.1)
Asian	46 (17.7)
African-American	9 (3.5)
Hispanic	97 (37.3)
Other	48 (18.5)

* First day of illness is defined as the first day of fever.

subjects met criteria for incomplete KD either by laboratory criteria or abnormal baseline echocardiogram. The median days of illness was 6.8, with the first day of illness defined as the first day of fever. The median age in this study was 2.8 years (IQR 1.5–4.9 years), and 160 (61.5%) subjects were male.

Approximately half (47.7%) of the subjects received sedation with chloral hydrate as they were younger than 3 years old. Thirty-four (13%) of the 260 subjects had an IVIG infusion reaction. Of these, 26 (76.5%) had chills, 3 (8.8%) had hypotension, and 5 (14.7%) had both chills and hypotension (Figure 1). There were no subjects who had an anaphylactic reaction. Patients with KD receiving IVIG are not routinely given premedication at our institution. If a patient had an infusion reaction, interventions included slowing or temporary discontinuation of the infusion (per provider's clinical judgement), as well as symptomatic therapy with a normal saline bolus, diphenhydramine, and/or acetaminophen. IVIG infusion was interrupted in all subjects once a reaction was identified. All of the KD subjects experienced their infusion reactions within 4 hours of starting their IVIG infusion (Figure 2). Two of these subjects had infusion reactions 2 hours into receiving IVIG and then subsequently received sedation at 7.3 and 9.7 hours into the IVIG infusion without further issues. Two subjects with a delayed infusion reaction experienced fevers/chills without any decrease in BP within 4 hours of their IVIG infusion. They both improved with a temporary interruption of their IVIG infusion. In 79.4% (27/34) of these children in whom IVIG infusion was interrupted, the IVIG infusion was restarted within 2 hours of stopping or slowing the infusion. Of the remaining 6 subjects, 3 restarted their IVIG within 3 hours of stopping the infusion and 3 subjects did not have their IVIG restart time documented. All KD subjects were able to restart their IVIG infusions and complete the entire IVIG dose of 2 g/kg.

The median time to administer sedation was 10.4 hours (IQR –4.7 to 13.6 hours) after the start of an IVIG infusion. Thus, the majority of subjects had completed

Figure 1. Flowchart of sedation and IVIG infusion reactions in patients with KD.

their IVIG infusions by the time they received sedation. Of the subjects who received sedation, 17.7% (22/124) received sedation while their IVIG was infusing. All of these subjects were able to complete their infusion without an IVIG infusion reaction during sedation.

Discussion

Currently there is no consensus on the optimal time to safely give sedation for an echocardiogram when a patient is concomitantly receiving IVIG. Previous studies have shown that it is important for children with KD to get an echocardiogram early to help direct medical management.² Sedation is associated with improved visualization of the coronary arteries.⁶ We evaluated when the majority of IVIG infusion reactions occurred, in the context of our hospital protocol, where a dose of IVIG 2 g/kg is slowly ramped up with maximum IVIG rate reached at 1.5 hours and an infusion is usually completed within 10 hours.

As expected, the majority of IVIG infusion reactions occurred early. All reactions occurred within 4 hours of starting the IVIG infusion. It is important to note that no infusion reactions occurred during sedation, though many patients received sedation after their IVIG had been completed. The majority of patients were able to resume their IVIG infusion or increase their infu-

sion rate within 3 hours of their infusion reaction, and all patients were able to complete their IVIG infusion with no complications post infusion reaction. None of the KD subjects who received sedation during IVIG infusion had an adverse effect either attributable to sedation or IVIG.

We recognize several strengths and weaknesses of this project. Strengths included being the largest study to evaluate the timing of immediate IVIG infusion reactions in KD. We do recognize that our electronic medical record has evolved over the 3-year study period, resulting in changes in location for documentation of infusion reactions and interventions. This raised the possibility that data were incomplete. Another limitation includes the small sample size. Furthermore, only 2 KD subjects who had IVIG infusion reactions received sedation and IVIG concomitantly after the IVIG infusion reaction had occurred.

Conclusions

In this study, 34 (13%) subjects had IVIG infusion reactions with the most common reactions being chills or hypotension. All episodes of hypotension and IVIG infusion reactions occurred within 4 hours after initiation of the infusion. Of the subjects who received sedation, no one had an IVIG infusion reaction while receiving

Figure 2. Timing of IVIG infusion reactions.*

* All infusion reactions occurred within 4.03 hours of starting IVIG.

sedation. It is important for clinicians to appreciate that most IVIG infusion reactions occur in the first 4 hours of administration. Therefore, echocardiography, even if requiring sedation in a young child, should not be delayed in someone being evaluated for KD.

ARTICLE INFORMATION

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