Rapid Rate Intravenous Immunoglobulin Administration: Safety Outcomes in 11,334 Infusions

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ABSTRACT

A national home infusion services provider (KabaFusion, LLC) has traditionally administered intravenous immunoglobulin (IVIG) at conservative maximum infusion rates to minimize adverse drug reactions (ADRs). The objective of this retrospective, observational study was to identify the impact of increased on-label infusion rates of a specific, high-purity product (Octagam) on patient safety. The study included all patients who received IVIG over a 10-year period. The study population was composed of both adult and pediatric patients with neuroimmune, neuromuscular disorders and primary immune deficiency diseases warranting IVIG treatment. Patients were divided into two randomized groups to provide an even distribution for analysis: those who received IVIG infusions at a rate of <110 mL/hr (Group 1) and those who received IVIG at ≥110 mL/hr (Group 2). There were 489 patients identified for inclusion in Group 1 (n=245) and Group 2 (n=244). Demographics (gender and age) and exposure (number of infusions) were similar between both groups.

The study data included 11,334 total IVIG infusions with a total of 282 ADRs (2.5%). The total number of ADRs (1.3% vs. 3.7% in Group 1, $p<0.0001$) and the number of patients with ADRs (10.7% vs. 31.0% in Group 1, $p<0.0001$) in the high infusion rate group (Group 2) were significantly lower. Based on these results, high infusion rates of specific high-purity IVIG products were associated with a significantly lower amount (both statistically and clinically) of non-serious and serious ADRs in both the adult and pediatric populations. These results can be of great utility in clinical application, if applied within the manufacturer's recommended guidelines, to ease the burden of time required for patients undergoing IVIG infusions.

Keywords: *patient safety, all neuromuscular disease, harm/risk analysis, IVIG, Octagam*

Introduction

High-dose IVIG therapy is accepted as an effective and well-tolerated treatment of neuroimmune and neuromuscular disorders as well as primary immune deficiency diseases (PIDD). It has been estimated that neurologic indications account for up to 43% of IVIG used in clinical practice.[1] Clinical trials have shown that IVIG can be infused at high rates without compromising safety, which is especially beneficial in patients with neuroimmunologic disorders who often receive high-dose IVIG in clinical practice.[2,3] Currently, high-dose IVIG therapy for neuroimmune disorders is defined as >1.0 g/kg per month, compared with low-dose IVIG therapy used for patients with PIDD (0.1-0.4 g/kg per month).[4,5] Though the use of IVIG can yield positive clinical outcomes, its administration can lead to different types of ADRs, most of which are mild, transient, and non-serious.[4-7] Prior studies have evaluated the administration of high-dose IVIG within different patient groups with neuroimmune and immunological diseases.[4-7] However, safety remains a concern with the use of IVIG administered at rapid rates.

KabaFusion, a national, patient-centered home infusion pharmacy within the United States (U.S.), has traditionally administered IVIG at conservative maximum rates to minimize ADRs. However, the total time and cost required to infuse IVIG therapy at lower rates may be burdensome for patients and healthcare providers, particularly for patients with neuroimmune disorders receiving high-dose IVIG regularly. If infusion rates can be safely increased, this could represent both a time- and cost-saving measure that would benefit patients and providers.[4,7] An internal audit prior to this study revealed the mean infusion rate for patients receiving IVIG at KabaFusion was 124 mL/hr. However, following the assessment of recommended standard rates for a high-purity IVIG product (Octagam), with infusion rates up to 504 mL/hr in a 70-kg patient,[8,9] as well as an assessment of industry standards, KabaFusion determined that an evaluation of infusion rates, and corresponding safety outcomes, could potentially add value to the current literature and provide clinical information for healthcare providers. The objective of this study was to identify the impact on patient safety of increasing on-label infusion rates[8,9] of a specific, high-purity IVIG product (Octagam).

Methods

Study Design and Patient Selection

A retrospective, observational study was conducted using adult and pediatric patient medical data collected

from KabaFusion from March 1, 2008 to May 31, 2018. Patients were included if they received IVIG infusions of Octagam 5% or Octagam 10%, at differing rates, abiding by the manufacturer's recommendations for maximum infusion rates of 294 mL/hr and 504 mL/hr (in a 70-kg patient), respectively.[8,9] Patients were excluded if they did not receive one full IVIG infusion of Octagam. Patients who met the criteria for inclusion were further divided into two groups with different IVIG infusion rates: Group 1 (<110 mL/hr) and Group 2 (≥110 mL/hr). Baseline characteristics (age, gender, diagnoses, and comorbidities) were collected, and retrospective patient data were evaluated.

Safety Outcomes

ADRs were collected from the KabaFusion electronic medical record (EMR) for all eligible patients and were further categorized into non-serious and serious categories. Serious adverse drug reactions (SADRs) were defined as any event in which a patient required urgent care, an emergency room (ER) visit, or hospital admission. The primary endpoint of the study was the comparison of ADRs in patients receiving IVIG at lower maximum infusion rates (Group 1: <110 mL/hr) with ADRs in those receiving IVIG at higher maximum infusion rates (Group 2: ≥110 mL/hr). The ADRs were those experienced by patients and subsequently evaluated and documented by registered nurses (RNs) and/or medical providers (MDs). Each ADR type experienced by a patient was considered one event. The data were then evaluated to determine the safety of increasing infusion rates with a specific high-purity IVIG product.

Statistical Analysis

Unadjusted descriptive statistics, including mean, standard deviation (SD) for continuous variables, and percentages for categorical variables were conducted to summarize the baseline characteristics between the two study groups. Statistical differences between the two study groups were tested using Student's t-test for continuous variables and using chi-square and Fisher's exact tests for categorical variables. Analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC). An unpaired, two-sided *P* value <0.05 was considered statistically significant.

Data Availability

Anonymized data not published within this article will be made available to any qualified investigator following a request to the corresponding author.

Results

Study Population

There were 489 patients identified for inclusion: Group 1 with infusion rates of <110 mL/hr (n=245) and Group 2 with infusion rates of ≥110 mL/hr (n=244). Patients were matched in terms of prior history of allergies, then similarly distributed within both groups in terms of gender (male [45%], female [55%]), age [mean=59 years], and number of infusions (Table 1). Per baseline diagnoses, chronic inflammatory demyelinating polyradiculoneuropathy (CIPD) was found to be >30% in both groups. Evaluating the baseline comorbidities, Group 2 had higher rates of concomitant comorbidities than Group 1, such as obesity (body mass index [BMI] >35 kg/m^2) (14.3% vs. 11.0%, p=0.0182), hypertension (11.9% vs. 7.3%, p=0.0329), history of arrythmia (6.1% vs. 2.9%, p<0.001), and coronary artery disease (2.0% vs. 0.8%, p=0.0127), respectively (Table 1).

Safety Outcomes

Patients eligible for inclusion received 11,334 total IVIG infusions (Group 1: 5,736; Group 2: 5,598). The

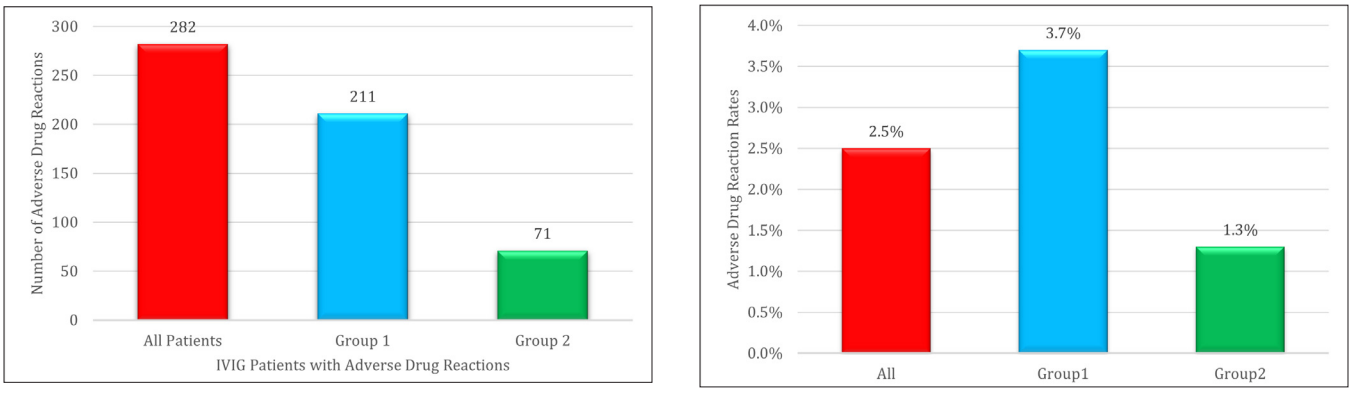

Figure 1. Adverse drug reactions: Number and rates per infusion (%). **P value <0.05 is considered statistically significant*

Table 1. Baseline patient characteristics

Characteristic	All Patients	Group 1 (<110 mL/hr)	Group 2 (≥110 mL/hr)	*P Value*
	n=489	**n=245**	**n=244**	
Male, n (%)	221 (45%)	111 (45%)	110 (45%)	0.8281
Female, n (%)	268 (55%)	134 (55%)	134 (55%)	
Age, Years, Mean (Range)	59 (10-95)	61 (10-91)	58 (14-95)	0.7102
Number of Infusions	11,334	5,736	5,598	
Infusion Rate - mL/hr, Mean (Range)	127 (20-480)	92 (20-108)	163 (110-480)	
Diagnosis, n (%)				
CIDP	165 (33.7%)	88 (35.9%)	77 (31.6%)	0.0526
Myasthenia Gravis	88 (18.0%)	36 (14.7%)	52 (21.3%)	<**0.0001**
PIDD	40 (8.1%)	19 (7.8%)	21 (8.6%)	0.8129
Pemphigus/Pemphigoid	26 (5.3%)	12 (4.9%)	14 (5.7%)	0.4291
GBS	24 (4.9%)	13 (5.3%)	11 (4.5%)	0.8201
Dermatopolymyositis/Polymyositis	24 (4.9%)	15 (6.1%)	9 (3.7%)	**0.0281**
Other Polyneuropathy/Neuropathies	21 (4.3%)	16 (6.5%)	5 (2.0%)	<**0.001**
Multiple Sclerosis	14 (2.9%)	5 (2.0%)	9 (3.7%)	0.7235
Stiff-Person Syndrome	10 (2.0%)	5 (2.0%)	5 (2.0%)	0.8216
Other	77 (15.7%)	36 (14.7%)	41 (16.8%)	0.2011
Comorbidities, n (%)				
Diabetes Mellitus	71 (14.5%)	35 (14.3%)	36 (14.8%)	0.7211
Obesity (BMI >35 kg/m^2)	62 (12.7%)	27 (11.0%)	35 (14.3%)	**0.0182**
Hypertension	47 (9.6%)	18 (7.3%)	29 (11.9%)	**0.0329**
Coagulation Disorder	40 (8.2%)	18 (7.3%)	22 (9.0%)	0.5298
Migraine	36 (7.4%)	19 (7.8%)	17 (7.0%)	0.8821
Arrythmia	22 (4.5%)	7 (2.9%)	15 (6.1%)	<**0.001**
Renal Disease	19 (3.9%)	8 (3.3%)	11 (4.5%)	0.6121
COPD	17 (3.5%)	12 (4.9%)	5 (2.0%)	0.0619
Immobility	9 (1.8%)	2 (0.8%)	7 (2.9%)	**0.0139**
CHF	7 (1.4%)	3 (1.2%)	4 (1.6%)	0.8214
CAD	7 (1.4%)	2 (0.8%)	5 (2.0%)	**0.0127**
CVA	3 (0.6%)	2 (0.8%)	1 (0.4%)	0.5201

CIPD=chronic inflammatory demyelinating polyradiculoneuropathy; PIDD=primary immune deficiency disorder; GBS=Guillain-Barré syndrome; Dx=diagnosis; BMI=body mass index; COPD=chronic obstructive pulmonary disease; CHF=congestive heart failure; CAD=coronary artery disease; CVA= cerebrovascular accident. A *P* value of <0.05 was found to be statistically significant.

mean infusion rate was 92 mL/hr (range: 20-108 mL/hr) for Group 1 and 163 mL/hr (range: 110-480 mL/hr) for Group 2 (Table 1). The total number of ADRs for all 11,334 infusions was 282 (2.5%) (Figure 1A). The total number of ADRs (71 vs. 211 in Group 1, p<0.0001) and the number of patients with ADRs (10.7% vs. 31.0% in Group 1, p<0.0001) were lower in the high infusion rate group, Group 2 (Figure 1B & Figure 2). The most common, non-serious ADRs included nausea, vomiting, increased blood pressure, blisters, pruritus, and tachycardia. Of the non-serious ADRs, nausea, rash, increased blood pressure, and fatigue were shown to be significantly less in the high infusion rate group, Group 2 (Table 2, p<0.05). The most common SADRs were headache, nausea/vomiting, chills, gastrointestinal (GI) events, flu-like symptoms, and shortness of breath. Of the SADRs, headache, fever/chills, and urticaria were shown to be significantly less in the high infusion rate group, Group 2 (Table 2, p<0.05). There were no deaths reported due to SADRs.

Table 2. Adverse drug reactions

Characteristic	All Patients	Group 1 (<110 mL/hr)	Group 2 (≥110 mL/hr)	*P Value*
	n=489	n=245	n=244	
Total Number of Infusions with ADR, n (%)	276 (2.4%)	205 (3.6%)	71 (1.3%)	<**0.0001**
Total ADR Number	282	211	71	<**0.0001**
ADR Rate	2.5%	3.7%	1.3%	<**0.0001**
Number of Patients with ADR	102 (20.9%)	76 (31.0%)	26 (10.7%)	<**0.0001**
Headaches	57 (11.7%)	40 (16.3%)	17 (7%)	**0.0013**
Nausea	27 (5.5%)	20 (8.2%)	7 (2.9%)	**0.0104**
Rash	34 (7%)	26 (10.6%)	8 (3.3%)	**0.0014**
Increased Blood Pressure	17 (3.5%)	14 (5.7%)	3 (1.2%)	**0.0113**
Vomiting	7 (1.4%)	5 (2%)	2 (0.8%)	0.4497
GI ADR/Diarrhea	3 (0.6%)	3 (1.2%)	0 (0%)	0.2485
Pain (any, body, muscle, generalized)	16 (3.3%)	12 (4.9%)	4 (1.6%)	0.0721
SOB/Wheezing	3 (0.6%)	2 (0.8%)	1 (0.4%)	1
Urinary Tract Infection	0 (0%)	0 (0%)	0 (0%)	-
Pruritis	7 (1.4%)	4 (1.6%)	3 (1.2%)	1
Flu-like Symptoms	5 (1%)	4 (1.6%)	1 (0.4%)	0.7243
Fever/Chills	17 (3.5%)	13 (5.3%)	4 (1.6%)	**0.0452**
Tachycardia/Palpitation	5 (1%)	2 (0.8%)	3 (1.2%)	0.6856
Dizziness/Vertigo	3 (0.6%)	3 (1.2%)	0 (0%)	0.2485
Neuropathy	4 (0.8%)	4 (1.6%)	0 (0%)	0.1235
Fatigue/Tiredness	19 (3.9%)	15 (6.1%)	4 (1.6%)	**0.017**
Poor Appetite	2 (0.4%)	2 (0.8%)	0 (0%)	0.499
Chest Pain/Tightness	14 (2.9%)	10 (4.1%)	4 (1.6%)	0.1733
Urticaria	34 (7%)	26 (10.6%)	8 (3.3%)	**0.0021**
Blurry Vision/Photosensitivity	3 (0.6%)	3 (1.2%)	0 (0%)	0.2485
Swelling/Edema	3 (0.6%)	2 (0.8%)	1 (0.4%)	1
Aseptic Meningitis	2 (0.4%)	1 (0.4%)	1 (0.4%)	1

ADR=adverse drug reaction; GI=gastrointestinal; SOB=shortness of breath. A *P* value of <0.05 was found to be statistically significant.

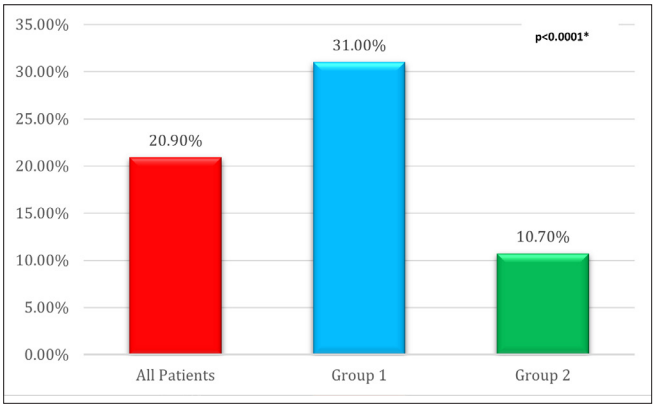

Figure 2. Percentage of Patients with Adverse Drug Reactions Compared with All Patients Who Received IV Immunoglobulin Infusions. *P value <0.05 is considered statistically significant

Discussion

This study was conducted to add evidence and valuable safety information to support informed decision-making by healthcare providers, especially those treating neuroimmune patients receiving high-dose IVIG. This study is extremely unique for multiple reasons. This study is conducted on a significantly large population of 489 patients, treated with multiple high-dose IVIG infusions and representing over 11,334 infusions conducted over a 10-year period. Additionally, the study focuses on both adult and pediatric populations from 10 to 95 years of age, therefore representing an unprecedented, wide age range. It also includes a large spectrum of neurological and immunological disorders. By way of comparison, the pivotal,

multicenter trial for Octagam in immune thrombocytopenic purpura (ITP) had 116 patients and only accounted for the adult population.[9]

In this study, >70% of the patients presented with neuroimmune/neuromuscular disorders, and widespread use of IVIG in this patient population has prompted awareness of ADRs (both non-serious and serious).[4-7] Because the effectiveness and safety of IVIG therapy are of primary concern, healthcare providers (including those from KabaFusion) have developed specific premedication regimens, including analgesics, antihistamines, and anti-inflammatory agents, to help prevent the occurrence of potential ADRs.[5-7] As a result, all of the patients in the current study received premedication prior to their IVIG infusion; by contrast, in the pivotal trial for Octagam, premedication was offered to patients but was only administered in one patient.[9]

Patients in Group 1 and Group 2 were found to have some differences in the types of ADRs reported. This could possibly be associated with specific patient characteristics and comorbidities. The study results have been stratified on the basis of multiple factors, including allergy history, age, and gender, to allow for a robust analysis. Nevertheless, patient outcomes were analyzed based on each patient's individual profile. It is also important to note that patients with neurological disorders tend to be associated with multiple comorbidities and with more complicated patient profiles (Table 1).

KabaFusion used data gathered over a period of 10 years and evaluated the impact of increased on-label infusion rates on patient safety. In a prior study, conducted by Rigas et al., the overall ADR rate per infusion was 4.7%.[4] In the current study, the overall ADR rate was 2.5%, with a higher ADR rate for slower IVIG infusions (3.7% vs. 1.3%, $p<0.0001$). Furthermore, the percentage of patients with ADRs who were receiving slower IVIG infusions was higher than in those receiving high-rate IVIG administration (31% vs. 10.7%, $p<0.0001$). Based on these results, infusion rates of specific high-purity IVIG products were associated with a significantly lower amount (both statistically and clinically) of non-serious and serious ADRs in both the adult and pediatric populations. These results can be of great utility in clinical application if applied within the manufacturer's recommended guidelines, to ease the burden of time required for patients undergoing IVIG infusions.

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Author Contributions

All authors: conception, organization, execution of the research described in the manuscript, statistical analysis, result interpretation, in addition to review and critique of the manuscript.

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Conflict of Interest

Dr. Rashid, Dr. Rigas, Dr. Piracha, and Dr. Alqadri report no disclosures.

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References

1. Perez EE, Orange JS, Bonilla F, et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol*. 2017;139:S1-S46.

2. Kriván G, Königs C, Bernatowska E, et al. An open, prospective trial investigating the pharmacokinetics and safety, and the tolerability of escalating infusion rates of a 10% human normal immunoglobulin for intravenous infusion (IVIg), BT090, in patients with primary immunodeficiency disease. Vox Sang. 2015;3:248–256

3. Sleasman JW, Duff CM, Dunaway T, et al. Tolerability of a new 10% liquid immunoglobulin for intravenous use, Privigen, at different infusion rates. *J Clin Immunol*. 2010;30:442–448.

4. Rigas M, Tandan R, Sterling RJ. Safety of liquid intravenous immunoglobulin for neuroimmunologic disorders in the home setting: a retrospective analysis of 1085 infusions. *J Clin Neuromusc Dis*. 2008;10:52-55.

5. Souayah N, Pahwa A, Burawski L, et al. A retrospective analysis of the safety profile of intravenous immunoglobulin in 1176 patients receiving home infusion therapy. *J Clin Neuromusc Dis*. 2018;19:181-195.

6. Souayah N, Pahwa A, Burawski L, et al. The safety profile of home infusion of intravenous immunoglobulin in patients with neuroimmunologic disorders. *J Clin Neuromusc Dis*. 2011;12:S1-S10.

7. Sparado G, Vultaggio A, Bosia A, et al. Rapid infusions of human immunoglobulin 50 g/l are safe and well tolerated in immunodeficiencies and immune thrombocytopenia. *Intl Immunopharm*. 2017;44:38-42.

8. Octagam 5%. Human Normal Immunoglobulin. Solution for Infusion. Prescribing Information, Octapharma.

9. Octagam 10%. Human Normal Immunoglobulin. Solution for Infusion. Prescribing Information, Octapharma.