Transfusion and Apheresis Science xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Unified infusion rates for 10% intravenous immunoglobulin

Philip Crispin[a,b,c,*], Maria Burgess[a], Amy Beath[a]

[a] Canberra Hospital ACT Health, Blood Counts Program Garran ACT 2606, Australia
[b] Haematology Department, Garran ACT 2606, Australia
[c] John Curtin School of Medical Research, Australian National University Acton ACT 2601, Australia

ARTICLE INFO

Article history:
Received 20 December 2017
Received in revised form 19 February 2018
Accepted 21 February 2018
Available online xxx

Keywords:
Intravenous immunoglobulin
Transfusion
Infusion
Adverse
events
Hemovigilance

ABSTRACT

Although manufacturers recommend varying infusion rates for differing intravenous immunoglobulin products (IVIg), there may be improved efficiency and reduced potential for error with the application of a single infusion policy for all IVIg products. During the transition from a 6% to a 10% IVIg, we prospectively evaluated patient reported adverse reactions to IVIg with the 10% product (Intragam 10) given at a rate faster than recommended by the manufacturer. While there was a significant increase in the rate of immediate infusion reactions when compared with the previous IVIg preparation (Intragam P), there was no increase in the rate of reactions post infusion. The rate of reactions was within previously reported expectations for other IVIg products. All reactions were minor, requiring no or minimal intervention and few impacted significantly on the quality of life. Despite an active haemovigilance program, minor adverse reactions were generally not reported. Our results suggest that a fast single rate of IVIg infusion is safe, and may minimise patient attendance and hospital resources with acceptable safety. In implementing a strategy to increase IVIg infusion rates an active process to monitor safety is preferred over standard haemovigiliance or pharmacovigilance processes.

1. Introduction

Intravenous immunoglobulin (IVIg) is a human derived blood product, produced by fractionation of pooled donor plasma to isolate immunoglobulin G (IgG). There are a variety of commercial manufacturing processes used, and different stabilisers added to immunoglobulin [1]. Therefore each product undergoes registration trials individually. Licensing agencies usually adopt for clinical use the protocols and procedures tested in trials during drug development, and as such each IVIg product may have a different recommendation for infusion. These are often complex, usually beginning slowly and escalating at different rates with variations in the intervals between incrementing the rates and maximal infusion rates.

Adverse reactions to IVIg include infusion reactions with fever, chills, myalgia and allergic or anaphylactic reactions. ABO blood group antibody mediated haemolysis, renal impairment, increased thrombotic risk, headaches and aseptic meningitis may be noted post-infusion. During infusion it is common practice to slow the infusion rate in the event of an adverse event, an intervention which often enables the completion of the infusion without further incident [1]. It is also known that people stable on one IVIg product are more likely to react following a transition to a new product, although the mechanism for this is unknown [2]. While it is possible that selection of the cohort prior to transition towards a product they can tolerate may contribute to this finding, the reduced rate of reactions found when people who have transitioned to a new IVIg continue on it, suggests the development of a degree to tolerance by individuals to the new product.

These issues favour the use of slower infusion rates in registration trials, taking a cautious approach to minimise the risk of the product being seen as inferior due to a higher rate of adverse reactions. By contrast, having a single IVIg infusion rate in the clinic enables efficiency in staff education and reduces the risk of inadvertent error with multiple complex infusion strategies. Faster rates also lead to improved efficiency in the clinic, reducing health care utilisation by improving patient flow.

In Australia, IVIg demand exceeds the supply obtained from local blood donors and there are a variety of products available, which are allocated to people based on their condition and the need to maintain a national inventory of locally sourced and imported products [3]. Patients are generally kept on the same product once allocated, unless there is a change in the contracted manufacturers or the manufacturing process, or a clinical indication to change product.

* Corresponding author.
E-mail addresses: Philip.crispin@act.gov.au (P. Crispin), Maria.burgess@act.gov.au (M. Burgess), Amy.beath@ct.gov.au (A. Beath).

https://doi.org/10.1016/j.transci.2018.02.023
1473-0502/

Table 1
Infusion protocol for 10% intravenous immunoglobulins. The infusion starts at a slow rate for 30 min (0.5 ml/kg/h for naïve patients or 1.0 ml/kg/h for subsequent doses), and is then increased every 15 min to the maximum rate of 7 ml/kg/hr. The rate of infusion is calculated in the table in ml/h based on weight for ease of use at the bedside.

Infusion Time (min)	Rate of infusion (mL/Kg/h)		Weight in Kg												Observations
			10	15	20	25	30	35	40	50	60	70	80	90	100	
First 30 min	0.5	or	5	7.5	10	12.5	15	17.5	20	25	30	35	40	45	50	Base line prior to commencing infusion
	1.0		10	15	20	25	30	35	40	50	60	70	80	90	100	
30–45	2		20	30	40	50	60	70	80	100	120	140	160	180	200	Every 15 mins for the first hour then Hourly and at completion of dose
45–60	4		40	60	80	100	120	140	160	200	240	280	320	360	400	
60–90	6		60	90	120	150	180	210	240	300	360	420	480	540	600	
90 to remainder	7		70	105	140	175	210	245	280	350	420	490	560	630	700	

The allocation of product initially assumes that they are generic and interchangeable, unless clinicians actively seek a particular product for a particular patient. There may potentially be a variety of infusion protocols following manufacturer recommendations in use at any one time.

In 2017, there was a transition from a 6% maltose stabilised product (Intragam P, CSL-Behring, Broadmeadows Australia [4]) to a 10% glycine stabilised product (Intragam 10, CSL-Behring, Broadmeadows Australia [5]), affecting approximately 60–70% of all IVIg recipients, with a disproportionate number of patients with chronic use due to immune deficiency being transitioned. In order to minimise the opportunity for error, patients were given our pre-existing IVIg 10% protocol (Table 1), which was different from the manufacturer's recommendations and enabled significantly faster infusions in most patients (163 v 209 min for a 70 kg person having 0.4 g/kg). We prospectively evaluated for infusion reactions during the transition from Intragam P to Intragam 10 in order to determine whether a higher infusion rate is safe.

2. Methods

Patients on long term intravenous immunoglobulin, for any indication, were invited to participate via a form sent out with Intragam P and given to them by their treating nurses in the first quarter of 2017, shortly prior to the expected transition from one product to another. All infusions were given at the higher rate, unless specifically directed otherwise by the treating clinician, whether patients participated in this study or not, in accordance with the hospital protocol. Premedication was not routinely given. If they consented to participate, they were ask to note whether they had any problems during, or after, the infusions. If pain was reported as a side effect, they were asked to rate the severity using a linear analogue scale, were 0 was no pain and 10 the worst pain imaginable. For all symptoms following infusion, participants were asked to rate the impact on their quality of life, to note any additional medications taken due to the symptoms and whether they required additional rest or time off work. Participants were asked to return the forms when they next returned for an infusion so that adverse events after the infusion could be recorded. Data from both Intragam P and Intragam 10 infusions were collected.

The rate of reactions during infusion and the rate of reactions after infusion were compared Intragam P and Intragam 10, the latter running at a faster rate than recommended by the manufacturer's guidelines. Reactions were analysed considering each infusion as a single event, and again by patient. A secondary analysis by infusion was planned excluding the first doses of Intragam 10, as reactions are known to be more common with the first dose of a new product. Further clinical information was obtained from the medical records where necessary.

Descriptive data were analysed assuming a non-parametric distribution and are presented as medians and range, unless otherwise specified. Comparisons between groups were made by Chi-squared tests or Fisher exact test when any expected value in the analysis was 5 or less. Data were analysed in SPSS v23 (IBM, CA). The study was approved by the ACT Health Low Risk Human Research Ethics Committee (approval number ETHLR.17.01).

Table 2
Frequency of adverse reactions to 10% intravenous immunoglobulin at faster rate, during and after infusions (n = 104).

Adverse event	Number of events occurring during infusions	Number of events occurring after infusions
Headache	6	8
Nausea	7	4
Generalised aches and pains	2	7
Fatigue	–	8
Chills	1	3
Fever	1	2
Light-headed		1
Unpleasant taste		1
Flushing		1
Renal angle pain		1
Burning in fingers	1	

3. Results

There were 78 patients identified having regular Intragam P, with 43 (55%) consenting to participate and returning at least one form (median 2, range 1–7). Of the participants, only 9 (22%) returned at least one report form for Intragam P and 41 reported on at least one infusions (range 1–7) with Intragam 10. There were 127 report forms returned, 104 for Intragam 10 (82%) and 23 for Intragam P (18%). The median age of participants was 60 years (range 20–87). The indications for IVIg were primary immunodeficiency (20, 46.5%), hypogammaglobulinaemia secondary to haematological malignancy (11, 22.6%) or other medical condition (2, 4.7%) or chronic neurological conditions as immune modification therapy (10, 23.2%). Doses administered ranged from 0.2 g/kg to 1 g/kg (median 0.4 g/kg), equating to total doses of 12.5–80 g/L (median 27.5 g/L).

During the infusion there were 20 (19%) reactions reported by patients during infusion with Intragam 10, compared with none during Intragam P ($p = 0.02$), and this remained significant when the first doses of Intragam 10 were excluded from the analysis. There were 26 patient reports of side effects in the days after infusion with Intragam 10 (25%) and 4 (17%) with Intragam P ($p = 0.59$). Reactions during infusion, subsequent to infusion or both were reported in 36 (35%) on Intragam 10 infusions and 4 (17%) with Intragam P and are summarised in Table 2.

Amongst the reactions during infusion there were seven reports including nausea, six with headache, two with generalised aches, two with pain along the arm having the infusion and one each with fever, rigors, rash and burning in the fingers. Of the patients reporting reactions during infusion, 10 (50%) also reported issues post infusion, in most cases of a similar nature. Only two patients with nausea during the infusion had post infusion problems, one with persisting nausea and the other with headache, indicating that nausea was self-limiting in most cases.

Please cite this article in press as: Crispin P, et al. Unified infusion rates for 10% intravenous immunoglobulin. Transfus Apheresis Sci (2018), https://doi.org/10.1016/j.transci.2018.02.023