ORIGINAL ARTICLE

A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions

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Aim: To document the incidence of immediate and delayed adverse events (AE) following intravenous immunoglobulin (IVIG) infusion in children.

Methods: Immediate and delayed adverse events were prospectively recorded for 345 infusions in 58 children receiving IVIG for immunodeficiency (n = 33) or immunomodulation (n = 25). For each infusion adverse events were documented during the infusion and by follow up interview 4-7 days later.

Results: Immediate adverse events occurred in 10.3% and delayed adverse events in 41.4% of children treated during the study period. Three and a half per cent of the infusions were associated with immediate AE and 20.9% with delayed adverse events. Headache was the most common delayed AE, occurring in 24.1% of patients and 12.8% of infusions.

Conclusions: Delayed adverse events to IVIG infusions are common in children. They occur more frequently than immediate adverse events and are the cause of significant morbidity. Recognition of the high frequency of delayed adverse events is important in the care of children receiving IVIG therapy.

The principal uses of intravenous immunoglobulin (IVIG) in paediatrics are for replacement therapy in immunodeficiency and immunomodulatory therapy in autoimmune and inflammatory conditions such as immune thrombocytopenic purpura and Kawasaki disease.^{1 2} IVIG is derived from pooled donor serum by ethanol fractionation with additional steps to remove immunoglobulin aggregates. Preparations are then stabilised using substances such as human albumin, glycine, polyethylene glycol, or sugars such as sucrose, maltose, or glucose.¹ As a result of fractionation and the addition of stabilisers, reactions may occur to either immunoglobulin aggregates or the stabilising agent. Steps to remove or minimise immunoglobulin aggregation reduced the immediate adverse event (AE) rate in children by approximately ninefold.³

Adverse events (AE) following IVIG infusions may be classified as immediate (occurring during the infusion itself) or delayed (occurring after the infusion has ceased).⁴ Infusion of IVIG preparations is associated with AEs such as fever, flushing, headache, rash, arthralgia, malaise, renal failure, aseptic meningitis, haemolysis, and anaphylaxis.^{1 2 5} The majority of the reactions observed are mild.^{1 2 5} There are few prospective studies of the prevalence of AEs in paediatric patients, and there is wide variation of the AE rate reported in the literature, ranging from less than 1% to as high as 40% of infusions in children.^{3 6-9} Children are generally considered to have a lower susceptibility to AEs than adults.¹⁰ To accurately quantify AEs, prospective recording of AE rates both per infusion and per patient treated is required.⁴ In this study we have prospectively examined the frequency of both immediate and delayed AE following IVIG infusion in children.

METHODS

Children and their parents undergoing IVIG infusions at The Children's Hospital at Westmead, Sydney, Australia during the 2002 calendar year were approached to enrol in the study. All agreed to participate. Patients received infusions for

immunodeficiency (n = 33) or for immunomodulation (n = 25) of autoimmune and inflammatory diseases. Thirteen of the 25 patients who received IVIG for immunomodulation had Kawasaki disease. Children treated with IVIG following bone marrow transplantation or those being treated for secondary immunodeficiency due to chemotherapy were not included. Three different preparations of IVIG were used during the study period—Intragam-P (CSL, Parkville, Melbourne, Australia), Sandoglobulin (ZLB Behring AG, Berne, Switzerland), and Intraglobin-F (Biotest AG, Frankfurt/Main, Germany). Consecutive infusions were studied with the date of infusion, child's weight, dose of IVIG administered, duration of the infusion, method of administration (central or peripheral line), and the administration of any pre-medication (corticosteroids or antihistamines) recorded.

Immediate AEs were observed by the nursing staff during the infusion and documented. These children were then reviewed by medical staff; if treatment or modification of the infusion was required, it was recorded as an AE.

Delayed reactions were assessed using a follow up interview with the parents or child (if over 12 years of age) between 4 and 7 days after the infusion. Contact was made by telephone in the majority of cases; a minority were interviewed in hospital. A questionnaire was administered. The parents/subjects were asked "Did you notice any problems after the immunoglobulin infusion?", followed by a list of common adverse effects (fever, headache, rash, abdominal pain, tiredness, nausea, vomiting) to which the respondents answered yes or no, followed by a final question regarding any other symptoms: "Was there anything else you noticed?". Delayed AE was defined as any event necessitating additional medical consultation or treatment, and/or requiring modification of any current therapy, and/or causing a significant loss of academic or leisure time. Significant loss was defined as an alteration of the child's normal activities,

Abbreviations: AE, adverse event; IVIG, intravenous immunoglobulin

e.g. attending school or completing homework, participating in extracurricular activities, sports, and playing with friends/siblings.

Seven patients received 15 episodes of repeat IVIG infusions over successive days as a treatment course. These infusions were treated as being discrete infusions for the purpose of assessing immediate AEs. Delayed AEs were considered to have been caused by the infusion that immediately preceded the event. Rates of AE were calculated per patient using only those with at least one infusion followed up, and per infusion using only those infusions with follow up.

Findings were analysed using the Mann-Whitney U test or Fisher's exact test.

The study was approved by the Ethics Committee of The Children's Hospital at Westmead.

RESULTS

Patients and infusions

Sixty patients ($n = 60$) were enrolled; 43 (71.6%) were male and 17 (28.4%) were female with a mean age of 4.03 years (range 0.3–13.9 years, SD 4.2 years). Adverse event data was available on 58 subjects; no data was available for two subjects with Kawasaki disease due to inability to contact the family within seven days of the infusion. Twenty six of the 58 subjects reported at least one adverse event (table 1).

The indications for infusion are shown in table 1 and are divided into two categories (immunodeficiency and immunomodulation). There were 404 infusions; data on immediate and delayed AE was collected in 345 (85.4%) infusions. The follow up was similar in both the immunodeficiency and immunomodulatory groups at 243/282 (86.2%) infusions and 102/122 (83.6%) infusions respectively.

One hundred and thirteen infusions were given through central venous lines (CVL) in 11 patients. Seven patients received a total of 46 doses of nitrous oxide, and one patient received 11 doses of midazolam as pre-medication for insertion of intravenous lines or CVL access. Anaesthetic administration did not make a significant difference to the AEs. The total number of patients with an AE was 26. Twenty four of these had experienced at least one AE prior to entering the study. Eight patients received intravenous corticosteroid prior to 51 infusions, and four patients received intravenous antihistamine prior to 17 infusions. Patients that were pre-medicated all had significant reactions to previous infusions. Pretreatment with steroids or antihistamines appeared to reduce but not eliminate AE. Considering subjects who had previous infusions with an AE, of the 17 subsequent infusions pretreated with antihistamine, seven (41.2%) had an AE; and of 51 subsequent infusions pretreated with corticosteroid, 24 (47.1%) had an AE.

The median dose of IVIG administered per treatment course in the immunodeficiency group was 0.48 g/kg compared to 0.51 g/kg in the immunomodulatory group (not significantly different; Mann-Whitney U test, $p = 0.27$). The median rate of infusion was higher in the

immunodeficiency group (0.17 g/kg/h) compared to the immunomodulatory group (0.13 g/kg/h) (Mann-Whitney U test, $p < 0.0001$).

Infusion related adverse reactions

Of the 345 infusions with complete follow up, 84 were associated with adverse events. Immediate reactions occurred in 6 (10.3%) and delayed reactions in 24 (41.4%) of the children. Twelve (3.5%) infusions were associated with immediate AE and 72 (20.9%) infusions with delayed AE. The majority (69.2%) of subjects with an AE had more than one infusion associated with an AE. There were no occasions of an immediate and delayed adverse event occurring in the same infusion.

In 59/404 infusions we were unable to obtain adequate follow up for delayed AE. The number of immediate AE in these (0/59) was not significantly different from the 12 immediate AE in the 345 infusions with follow up (0% v 3.5%; Fisher's exact test, $p = 0.15$). Where infusions were administered on consecutive days, the opportunity to record a delayed AE for preceding infusions was reduced to 24 hours. However, this applied only to a minority (15/404) of the infusions.

To examine whether the rate of infusion may be related to adverse events, we studied all subjects with at least one non-adverse event infusion followed by at least one adverse event infusion ($n = 16$). The median infusion rate for the first non-adverse event infusion during the study was 0.14 g/kg/h; the median infusion rate for the first subsequent adverse event was 0.17 g/kg/h. The adverse events were not clearly related to an increased rate of infusion as only 8/16 had a higher rate for the second infusion than the first infusion, one had an identical rate, and the rate was lower for the second infusion in 7/16.

Table 2 shows the types of immediate and delayed AE. The most commonly recorded immediate reactions were headache, pain at the infusion site, and vertigo. Headache was the most common delayed AE, occurring in 24.1% of patients and 12.8% of infusions. Fatigue, abdominal pain, and myalgia were also common. Sixty nine (72.6%) of the delayed reactions occurred within 24 hours of completing the infusion. A significant number of delayed reactions occurred after 24 hours: 10 between 24 and 48 hours, 6 between 48 and 72 hours, and 10 between 72 and 96 hours.

Immediate AEs were treated with a slowing of the infusion rate. Antihistamines were given for rashes, vertigo, and nausea. Paracetamol (acetaminophen) was given to patients with fever or headache. One severe immediate AE required cessation of the infusion. This was in a child with eosinophilic folliculitis and a past history of asthma who experienced chest pain and bronchospasm. Corticosteroid and bronchodilator were given. This child had had numerous previous infusions and received further infusions without complication.

In the present study, headache as an immediate AE was reported in only 0.9% of infusions and 5.2% of patients. Only

Table 1 Patients and rate of adverse event by diagnosis

Diagnosis	Total patients	Patients with AE (%)	Total infusions	Infusions followed up with AE (%)
Immunodeficiency				
CVID	21	15 (71.4)	178	48 (27.0)
X-linked agammaglobulinaemia	5	0 (0)	14	0 (0)
Other	7	3 (42.9)	51	12 (23.5)
Immunomodulation	25	8 (32.0)	102	24 (23.5)
Overall	58	26 (44.8)	345	84 (23.5)

AE, adverse event; CVID, common variable immunodeficiency.

Table 2 Immediate and delayed adverse events by patient (n = 58) and by infusion (n = 345)

Adverse event	Patients with adverse events (%)*			Infusions with adverse events (%)*		
	Overall	Immediate	Delayed	Overall	Immediate	Delayed
Headache	15 (25.9)	3 (5.2)	14 (24.1)	47 (13.7)	3 (0.9)	44 (12.8)
Fatigue	12 (20.0)	0	12 (20.7)	18 (5.2)	0	18 (5.2)
Abdominal pain	8 (13.8)	0	8 (13.8)	8 (2.3)	0	8 (2.3)
Myalgia	4 (6.7)	0	4 (6.7)	8 (2.3)	0	8 (2.3)
Nausea	4 (6.7)	1 (1.7)	3 (5.2)	4 (1.2)	1 (0.3)	3 (0.9)
Fever	4 (6.7)	1 (1.7)	3 (5.2)	4 (1.2)	1 (0.3)	3 (0.9)
Rash	4 (6.7)	1 (1.7)	2 (3.4)	9 (2.6)	1 (0.3)	8 (2.3)
Pain at infusion site	2 (3.4)	2 (3.4)	0	3 (0.9)	3 (0.9)	0
Vertigo	2 (3.4)	2 (3.4)	0	3 (0.9)	3 (0.9)	0
Arthralgia	2 (3.4)	0	2 (3.4)	2 (0.6)	0	2 (0.6)
Palpitation	1 (1.7)	1 (1.7)	0	2 (0.6)	2 (0.6)	0
Bronchospasm	1 (1.7)	1 (1.7)	0	2 (0.6)	2 (0.6)	0
Plantar fasciitis	1 (1.7)	0	1 (1.7)	1 (0.3)	0	1 (0.3)
Chest pain	1 (1.7)	1 (1.7)	0	1 (0.3)	1 (0.3)	0
Overall				112	17	95

*Percentages given are for patients and infusions with follow up.

one of the immediate headaches lasted longer than 24 hours; it had resolved by 48 hours. In contrast, headache was the most frequent delayed AE. Most (85.1%) of the delayed headaches resolved within 24 hours but they often resulted in significant modification of activity and required analgesic therapy. Seven episodes lasted longer than one day, with one patient with no past history of AE or headaches from unrelated causes reporting headache persisting for three days. Eight of 10 school days that were lost were due to headache. No patient required a lumbar puncture on account of the headache because of additional features (neck stiffness, photophobia, fever) suggestive of aseptic meningitis.

Intragam-P was administered in 346 infusions, Sandoglobulin in 53 infusions, and Intraglobin-F in 5 infusions. AE rates per number of infusions were 23.2% for Intragam-P and 34.9% for Sandoglobulin, which were not significantly different ($p = 0.13$, Fisher's exact test). Sandoglobulin was used for eight patients with troublesome AEs following Intragam P; however, six of the eight patients continued to have AE.

DISCUSSION

To our knowledge this is the first study to prospectively document the high rate of delayed AEs (20.9% of infusions and 41.4% of patients). Delayed AE were six times more frequent than immediate reactions per patient and four times more frequent per infusion. The previous lack of recognition of the significance of delayed AE indicates that unless these delayed symptoms are actively sought they are likely to be overlooked. In this study we have reported the data as both per patient and per infusion, as suggested by the FDA Center for Biologics Evaluation and Research,⁴ in recognition of the fact that AE rates per infusion are not necessarily independent events.

There are three previous prospective studies examining AEs in paediatric patients; however, none of these studies examined delayed adverse reactions. Al-Wahadneh and colleagues,⁷ in a study of 13 children with immunodeficiency, found an infusion AE rate of 14.5% in a total of 104 infusions. Aghamohammadi and colleagues¹¹ conducted a study restricted to immediate reactions in 1231 infusions in 35 patients over a period of seven years, the majority of whom were children. Although it is stated that this was a retrospective study, the data appear to have been prospectively recorded. The rate of immediate adverse reactions was 12%, with "chills" (59%) as the most common reaction. Galli and colleagues¹² reported an AE rate of around 40% in children treated for immunodeficiency prior to the introduction of low IgG aggregate formulations of IVIG. Benesch and

colleagues⁹ recently reported a relatively high infusion AE rate of 40% in children treated for immune thrombocytopenic purpura (ITP). Retrospective studies of children with hypogammaglobulinaemia by Skull and Kemp³ and ITP by Kattamis and colleagues,¹³ reported AE rates of 0.8% and 34% respectively. In prospective studies of immediate AE including both adults and children, Pautard and colleagues⁸ found a low rate of AEs occurring in 0.54% of infusions and 6.3% of patients, Eijkhout and colleagues¹⁴ found AEs in 5% of infusions and over 25% of patients, and Brennan and colleagues⁶ found AEs in 0.8% of infusions. We were able to obtain data on delayed AE in 85.4% of the infusions. The number of immediate AE in those infusions without follow up did not differ significantly from those with follow up, suggesting the lack of follow up had not introduced a significant bias into the findings.

Headache is consistently reported as an IVIG infusion AE. A prospective study of IVIG for neurological disease in adults found headache in 30% of treatment courses; however, the occurrence of delayed headaches was not recorded.¹⁵ The generally accepted rate of immediate headache during infusion is less than 5%.^{7, 8, 14} with rates of up to 81%¹⁶ reported in adults with neuromuscular disease, and up to 34% in children with ITP within 24 hours of infusion.¹³ Delayed headache was the most common AE and had a significant morbidity defined as a significant loss of academic or leisure time. Although this definition contains a subjective element, it does suggest a significant impact of the delayed AE on the child's daily activities. Previous studies have suggested that many AEs, especially headache, are infusion rate dependent.^{9, 16-18} These considerations may apply principally to immediate reactions, and as the majority of headaches in the present study were delayed it would seem less likely that delayed reactions are rate dependent.

No episodes consistent with aseptic meningitis (severe headache associated with fever, nuchal rigidity, photophobia, nausea, and cerebrospinal fluid pleocytosis¹⁹) were observed in our study. Aseptic meningitis has been reported at rates as high as 11% in adults¹⁹ with neurological disease and 5% in children with ITP.¹³ Aseptic meningitis following IVIG appears to be more common in patients with ITP, neurological disease, or a history of migraine.^{17, 19, 20} The aetiology of aseptic meningitis is uncertain, but it may be due to a hypersensitivity reaction to components of the IVIG preparation.^{19, 20} It is also possible that IVIG infusions trigger migraine, and migraine has been reported to be a risk factor for headaches following IVIG infusion.²⁰ Headache consistent with migraine was experienced by one child who developed three episodes of headache associated with photophobia.

What is already known on this topic

- AEs following IVIG infusions may be classified as immediate (occurring during the infusion itself) or delayed (occurring after the infusion has ceased)
- Delayed AE have not been prospectively documented

In conclusion, delayed adverse reactions to IVIG infusions are common in children and occur more frequently than immediate AEs. They were the principal cause of lost school time, need for additional therapies, and medical consultations in this study. Recognition of the high frequency of delayed AEs is important in the care of children receiving IVIG therapy.

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Competing interests: Professor Kemp was the author of a clinical expert report for CSL in 1997 and his superannuation fund owns some shares in CSL.

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What this study adds

- Delayed AE are more common than immediate AE
- Headache is the most common delayed AE, occurring in 24% of patients and 13% of infusions in this study