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CLINICAL REPORT

Not All Intravenous Immunoglobulin Preparations are Equally Well Tolerated

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Intravenous immunoglobulin (IVIG) is used for many indications beyond the original substitution in primary antibody deficiency. Whereas many reports mention adverse reactions, no comparative data exist concerning the incidence of side-effects among the different brands of IVIG. We describe here our experience with the use of different IVIG formulations and their tolerability in a select cohort of 40 patients. The IVIG dose ranged from 0.4 to 3 g/kg/day and was given for 1–2742 days. Fourteen patients (35%) experienced mild to severe adverse reactions during or within 48 h of administration of standard IVIG preparation, which did not recur after switching to an alternative preparation. Adverse reactions included headache, fever, chills, nausea, emesis, hypotension and muscle cramps. One patient experienced a severe adverse reaction; he had a 3-day headache following IVIG infusion. Among the 16 patients who received alternative preparation initially, none experienced adverse reactions. In conclusion, this study shows that IVIG preparations are not all equally well tolerated in patients. The data suggest that, perhaps to a comparable extent to the preparation itself, the infusion rate has a major effect. If a reduction in the infusion rate does not minimize side-effects, one should consider switching the IVIG formulation. ***Key words: intravenous immunoglobulin; adverse drug reaction; prevention; toxic epidermal necrolysis; hypogammaglobulinaemia; lung transplantation.***

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The range of diseases for which intravenous immunoglobulin (IVIG) is used has increased rapidly since its initial use in primary antibody deficiency (1, 2). Important reasons for this expansion in IVIG use are its effectiveness and safety. However, side-effects and adverse reactions do occur. Most adverse effects are mild and transient, including headaches, flushes, fever, chills, fatigue, nausea, diarrhoea, blood pressure changes and tachycardia. Although rare, serious and potentially fatal side-effects include anaphylactic reactions, aseptic meningitis, acute renal failure and thrombo-embolic complications, such as stroke and myocardial infarction (3).

Whereas many reports concentrate on adverse reactions following IVIG infusions (3–8), few studies have addressed the potential difference between the different IVIG preparations (2, 9, 10) and no comparative data exist concerning the incidence of side-effects among the different brands of IVIG. During our clinical practice, we have observed various IVIG formulations to be of different tolerability in our patients. The authors believe this is important clinical information for the practical use of IVIG, and we therefore report here our experience within an 8-year time-period.

MATERIALS AND METHODS

This retrospective observational study included paediatric and adult patients attending our dermatology department for the application of IVIG for various clinical indications between May 2001 and December 2008.

Patients characteristics and IVIG therapies

Forty patients (25 males, 15 females) were included in the study with a median age of 47 years (age range 15–73 years). Patient demographic data are displayed in Table SI (available from http://adv.medicaljournals.se/article/abstract/10.2340.00015555-3253/Tab1). The indications for IVIG included hypogammaglobulinaemia, cytomegalovirus (CMV) or Epstein Barr virus (EBV) mismatch in lung transplant recipients (25 cases), substitution for immunoglobulin G (IgG) deficiency (1 case), pemphigus vulgaris (1 case), dermatomyositis (2 cases), atopic dermatitis (1 case) and toxic epidermal necrolysis (TEN) (10 cases). EBV mismatch means different donor and recipient serological status for EBV, predisposing EBV-negative recipients of an EBV-positive graft to EBV infection and potentially post-transplant lymphoproliferative disease. Two IVIG preparations were predominantly used: Redimune NF Liquid® (CSL Behring AG, Bern, Switzerland) and Octagam® (Octapharma, Lachen, Switzerland). Two patients received Endobulin® (Baxter AG, Volketswil, Switzerland) after adverse reactions to Redimune®. The choice of primary IVIG preparation was a result of hospital management decision-making based primarily on availability and price, not on medical considerations. The total administration periods were 1952 patient-days for Redimune®, 20,759 patient-days for Octagam® and 7 patient-days for Endobulin® (see Table SI for exact dosages). Administration periods were calculated as the cumulative days on IVIG of all patients; for one patient the total duration

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of treatment was counted from the first to the last IVIG dose (including the days between 2 doses). The patients were not specifically instructed to drink before the infusions of all three products. Only the patients who had previous adverse events received NaCl infusion before IVIG, the other only had NaCl to keep the infusion open (500 ml/24 h). A screening process (anti-IgA antibodies) before IVIG administration was performed in chronic situations, but not for acute situations (TEN). IgA-deficient patients may form macromolecular complexes with anti-IgA antibodies of the recipient of IVIG that can lead to anaphylactic reaction. Anaphylaxis can be prevented by using IgA-depleted IVIG, even if it is still contaminated with a small amount of IgA. In our institution pre-medication is not given systematically before starting IVIG.

Classification of reaction

Reactions occurring during or within 48 h of IVIG infusion were classified as mild, moderate or severe, based on the classification of adverse reactions following IVIG proposed by Brennan et al. (11), and were defined as follows:

- Mild reactions include headache, fever, chills, nausea, emesis, hypotension and muscle cramps. These subside once the infusion rate is decreased.
- Moderate reactions include mild reactions worsening, necessitating discontinuation of the infusion.
- Severe reactions include moderate reactions persisting or becoming worse or other symptoms, such as tightness of the throat, severe shaking, severe breathlessness or wheezing, severe dizziness or fainting, sensation of chest tightness or collapse. A severe reaction would require the administration of adrenaline and further medical attention. Serious and potentially fatal side-effects also include, for example, anaphylactic reactions, aseptic meningitis, acute renal failure and thrombo-embolic complications, such as stroke and myocardial infarction (3).

Statistical methods

The proportion of adverse events was computed separately for each preparation of IVIG. For patients who had only one IVIG preparation, the rate of adverse events was compared using Fisher's exact test. For patients taking both Redimune® and Octagam®, the rate of adverse events was compared using McNemar's test. Analysis was performed using the R programming language (12).

Assuming that adverse events occur in 15% of patients treated with Redimune® as null hypothesis, our sample size of 28 patients who had been exposed to Redimune® has a power of 80% to detect the observed rate of 35% of patients experiencing any adverse event.

RESULTS

Thirteen patients (33%) experienced mild and moderate adverse reactions during or within 48 h of the administration of standard IVIG preparation (Redimune®), which did not recur after switching to an alternative preparation (Octagam® or Endobulin®). Of patients taking only one preparation (12 taking only Redimune®, and 12 taking Octagam®), four experienced adverse events, all with Redimune ($p = 0.09$, Fisher's exact test). For patients taking both Redimune® and Octagam® ($n = 14$), 8 experienced adverse events while on Redimune®, compared with no adverse events on Octogam® ($p = 0.004$, McNemar's test). Adverse reactions included headache (8 cases), fever (5 cases), chills (3 cases), nausea (3 cases), emesis (3 cases), hypotension (1 case) and muscle cramps (1 case). In four cases, the presence of predisposing conditions was identified: one patient experiencing severe headache had a history of migraine (No. 9); one patient with nausea and emesis also had a symptomatic hypercalcaemia with 133 mmol/l (No. 12); in two cases the presence of a concomitant infection was identified (status after treated gastroenteritis by patient No. 7, and suspicion of sepsis by patient with TEN (No. 25)). Except for two cases, adverse events occurred during the first or second infusion of a given preparation. One patient (No. 9) experienced severe adverse reaction. Among the 16 patients who received Octagam® initially, none experienced adverse reactions (see Table II in this article and Table SI).

The management of adverse reactions involved initial slowing of the infusion rate (of 50%) or stopping and restarting at a slower rate after symptoms had disappeared. The standard infusion rate for Redimune® was 0.5 ml/kg/h for the first 30 min, 0.75 ml/kg/h for a further 30 min, then 1 ml/kg/h for the rest of the infusion. Octagam was infused at 30 ml/h for the first 30 min, with an increase of 30 ml/h every 30 min until the end of the infusion, irrespective of body weight. Endobulin® was given at 0.5 ml/kg/h for the first 30 min, with an increase of 30 ml/h every 30 min until the end of the infusion. In addition, non-steroidal anti-inflammatory drugs (NSAIDs) were administered. In case of persisting symptoms, a switch to an alternative IVIG formulation was undertaken. The second product (Octagam® or Endobulin®, see Table II and Table SI)) was well tolerated in all cases. The immediate adverse reactions occurring during the infusion generally resolved upon slowing the infusion rate, except for 3 cases out of 14, where the infusion had to be stopped before the planned dose (Table SI), patient Nos. 5, 9 and 15). One patient (No. 9) experienced a 3-day headache following IVIG infusion, requiring hospital stay (in fact the only case in our series classified as a severe adverse reaction). The Redimune® infusion was stopped and the headache was treated symptomatically (with hydration and NSAIDs).

As all adverse reactions were observed on Redimune®, starting with patient No. 29, IVIG was initiated with Octagam® as first-line preparation (Table SI, Nos. 29–40). Patients No. 11 and 12, initiated on Redimune®, were subsequently switched to Octagam®. Furthermore,

Table II. *Numbers of patients and adverse events*

IVIG preparation	Patients treated, *n*	Adverse events, *n* (%)
Redimune NF Liquid®	28	14 (100)
Octagam®	26	0 (0)
Endobulin®	2	0 (0)

patient Nos. 1–10, initiated on Octagam®, which had been switched to Redimune® for lower drug costs, were put back on Octagam® to avoid further reactions. Seven of patient Nos. 1–10 had tolerated many infusions of Octagam® uneventfully, while experiencing adverse reactions when given Redimune® once. Only patient Nos 13 and 14, initially treated with Octagam®, who had been changed to Redimune®, continued to receive this preparation without adverse reactions. No dose-effect relationship was observed between IVIG dose and the severity of adverse events.

DISCUSSION

IVIG products differ regarding their constituents (preservatives and inhibitors of IgG aggregation) and physical/chemical characteristics (e.g. lyophilized powder or liquid and pH). According to the World Health Organization (WHO), preparations must contain at least 90% intact IgG with a normal IgG subclass distribution, as little IgA as possible, and no Ig fragments or aggregates. IgA-deficient patients may form macromolecular complexes with anti-IgA antibodies of the recipient of IVIG, which can lead to anaphylactic reaction. Anaphylaxis can be prevented by using IgA-depleted IVIG, even if it is still contaminated with a small amount of IgA (8). Measures taken by manufacturers to ensure the safety of the product include careful selection of donors, screening for infectious agents and the use of modern viral inactivation procedures (2, 13). IVIG products have a final concentration of 3–12% and contain 1% or less of the total IgG in small aggregates.

Although *in vitro* experiments (14) show no difference in the efficacy of different IVIG brands, no comparative data exist concerning the incidence of side-effects among the different brands of IVIG. Salt and sugar content, osmolality, total volume infused, rate of infusion, concentration, and total dose of IVIG infused, appear to be associated to some extent with the likelihood of side-effects (15). There are currently no tests or markers available to predict adverse reactions in a given patient and guide the choice of a particular IVIG product.

In a study including more than 200 patients receiving IVIG for different autoimmune diseases and nearly 10,000 infusions for relapsing-remitting multiple sclerosis patients, the occurrence of adverse effects was 24–36% after high-dose IVIG, most of which were headaches, while all were considered mild adverse events (3). In a prospective study of adverse reactions in 459 primary antibody-deficient patients receiving IVIG, mild or moderate adverse reactions occurred in 59 (12.9%) patients. The low rate of adverse events in comparison with our study (35%) and the one of Katz et al. (24–36%) are probably due to their selective inclusion criteria: only those having uneventfully received at least six infusions were included in the study by Brennan et al. (11).

Our experience shows that, in a selected patient cohort requiring IVIG substitution mostly for hypogammaglobulinaemia or CMV/EBV mismatches in lung transplant recipients and treatment of TEN, Redimune® proved more likely to induce adverse events than either Octagam® or Endobulin®. This phenomenon was observed repeatedly, even though manufacturer's instructions were followed exactly, including warming of the Redimune® to body temperature before infusion, except in one case. Adverse events were observed in such a consistent fashion that, despite higher drug costs, Octagam® was designated as first choice in lung transplant recipients.

Retrospectively, and considering that Redimune® was given at the maximal recommended rate, whereas Octagam® and Endobulin® were given at a lower rate than the maximum recommended, we consider the infusion rate to be a fundamental parameter in the administration of IVIG. The limitations of our study include the heterogeneous conditions treated, requiring different doses (as listed in Table SI). The general state of health of patients was heterogeneous, including lung transplant patients undergoing extracorporeal photopheresis for different indications (bronchiolitis obliterans syndrome, recurrent acute allograft rejection), as described previously elsewhere (16), intensive-care unit patients in the case of TEN, and patients with severe atopic dermatitis. Even if the high fever developed by a patient with TEN could easily be infection-associated rather than related to the IVIG infusion, the symptoms correlated chronologically at least in three of the four cases concerned. In one case the patient received a non-warmed Redimune® IVIG preparation. The main problem is that comparison between the different infusion rates is difficult, as different administration regimens were used, and the concentration of the products differed significantly. The administered doses correspond to the recommendations of the manufacturer; however, the maximal administration rate differed significantly between the three preparations. The standard infusion rate used in the patients in this sample and the maximum recommended infusion rate were the same for Redimune® (Table III). In comparison, the maximum infusion rate recommended for Octagam® is four-fold the standard infusion rate given and the maximum recommended infusion rate of Endobulin® is eight-fold the standard infusion rate (Table III). Accordingly, the concentrations of the products differ significantly. The patients were not specifically instructed to drink before the infusions of all three products. This may be of importance, as it is known that hydration of the patient is of outstanding importance and may explain why symptoms occurred with Redimune®, even though the recommended infusion rate was not exceeded.

Table III. *Characteristics of intravenous immunoglobulin products cited including properties and excipients that may account for side-effects (sugar and sodium content, osmolarity, pH and IgA content)*

	Redimune NF Liquid®	Octagam®	Endobulin®
Manufacturer or distributor	ZLB Bioplasma	Octapharma	Baxter
Formulation	Liquid	Liquid	Lyophilized
Reconstitution time (min)	None (liquid solution)	None (liquid solution)	Several
Available concentration (%)	12	5	5
Maximum recommended infusion rate (ml/kg/h)	1	4.2	8
Sugar content	None	100 mg/ml maltose	50 mg/ml ± 5 mg
Sodium content	<10 mmol/l	1.75 mg/ml	3 mg/ml ± 1 mg
Osmolarity	360 mOsm/kg	310–380 mOsm/kg	357 mOsm/kg
pH	5.3	5.1–6	7
IgA content	<100 μg/ml	<100 μg/ml	<50 μg/ml

Although our patients had a wide range of conditions, they were all seen within our dermatology department or in the intensive care unit, which may represent a selection bias. The indication for IVIG therapy itself may influence the type of adverse reactions: patients with neurological disorders are thought to present more cutaneous eczematous rashes following IVIG infusion (13), but our report does not include such indications for IVIG use.

As this is a retrospective case series, the adverse events were not recorded systematically. Whereas TEN patients are hospitalized for many days, atopic dermatitis and pemphigus patients, for example, receive their IVIG infusion on an outpatient basis, limiting our observation of adverse reactions to immediate adverse effects; therefore, adverse effects occurring subsequently may have been missed.

This study indicates that, despite common prophylactic measures, IVIG preparations are not all equally well tolerated in patients. However, the results suggest an influence of the infusion rate. Indeed, the present data suggest that the side-effects may be strongly associated with the infusion rate, which was not adapted to the concentration of the different products. This is supported by the observation that most of the adverse events resolved, or reduced, after lowering the infusion rate (cf. subsequent management, Table SI). In the case of mild adverse reactions in a given patient, one should first adapt the infusion rate to the body weight of the patient before, in a second step, considering substituting another IVIG preparation. Correct hydration of the patient should be ensured before therapy. In conclusion, this study shows that side-effects of IVIG are associated with the concentration of the product, and that the infusion rate has to be adapted.

The authors declare no conflict of interest.

REFERENCES

1. Ishii N, Hashimoto T, Zillikens D, Ludwig RJ. High-dose intravenous immunoglobulin (IVIG) therapy in autoimmune skin blistering diseases. Clin Rev Allergy Immunol 2010; 38: 186–195.
2. Prins C, Gelfand EW, French LE. Intravenous immunoglobulin: properties, mode of action and practical use in dermatology. Acta Derm Venereol 2007; 87: 206–218.
3. Katz U, Achiron A, Sherer Y, Shoenfeld Y. Safety of intravenous immunoglobulin (IVIG) therapy. Autoimmun Rev 2007; 6: 257–259.
4. Ballow M. Safety of IGIV therapy and infusion-related adverse events. Immunol Res 2007; 38: 122–132.
5. Bonilla FA. Intravenous immunoglobulin: adverse reactions and management. J Allergy Clin Immunol 2008; 122: 1238–1239.
6. Carbone J. Adverse reactions and pathogen safety of intravenous immunoglobulin. Curr Drug Saf 2007; 2: 9–18.
7. Hamrock DJ. Adverse events associated with intravenous immunoglobulin therapy. Int Immunopharmacol 2006; 6: 535–542.
8. Orbach H, Katz U, Sherer Y, Shoenfeld Y. Intravenous immunoglobulin: adverse effects and safe administration. Clin Rev Allergy Immunol 2005; 29: 173–184.
9. Hooper JA. Intravenous immunoglobulins: evolution of commercial IVIG preparations. Immunol Allergy Clin North Am 2008; 28: 765–778, viii.
10. Roifman CM, Schroeder H, Berger M, Sorensen R, Ballow M, Buckley RH, et al. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency. A randomized double-blind trial. Int Immunopharmacol 2003; 3: 1325–1333.
11. Brennan VM, Salome-Bentley NJ, Chapel HM. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. Clin Exp Immunol 2003; 133: 247–251.
12. R Development Core Team (2009). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. [cited 2009 Dec 9]. Available from: http://www.R-project.org.
13. Vecchietti G, Kerl K, Prins C, Kaya G, Saurat JH, French LE. Severe eczematous skin reaction after high-dose intravenous immunoglobulin infusion: report of 4 cases and review of the literature. Arch Dermatol 2006; 142: 213–217.
14. Zhang G, Lopez PH, Sheikh KA. Comparison of different brands of IVIg in an in vitro model of immune neuropathy. J Neuroimmunol 2006; 173: 200–203.
15. Nydegger UE, Sturzenegger M. Adverse effects of intravenous immunoglobulin therapy. Drug Saf 1999; 21: 171–185.
16. Benden C, Speich R, Hofbauer GF, Irani S, Eich-Wanger C, Russi EW, et al. Extracorporeal photopheresis after lung transplantation: a 10-year single-center experience. Transplantation 2008; 86: 1625–1627.