ADVERSE EFFECTS OF INTRAVENOUS IMMUNOGLOBULIN THERAPY IN PATIENTS WITH ANTIBODY DEFICIENCY

A. Aghamohammadi, A. Farhoudi, M. Moin, Zahra Pourpak, N. Rezaei, M. Nikzad, M. Movahedi, M. Gharagozlou, Lida Atarod, Akefeh Ahmadi Afshar, Nasrin Bazargan, K. Abolmaali and Maryam Mahmoudi

Department of Immunology and Allergy, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Long-term intravenous immunoglobulin (IVIG) infusion is an effective treatment for children with humoral immunodeficiencies, already be complicated by systemic adverse effects. In order to determine the adverse effects of intravenous immunoglobulin in patients with antibody deficiency, 45 immunodeficient patients receiving intravenous immunoglobulin were studied during a 36-month period at Children's Medical Center. The investigated group included 25 patients with common variable immunodeficiency, 14 patients with X-linked agammaglobulinemia and 6 patients with IgG subclass deficiency. A total of fifty adverse effects occurred through 955 infusions (5.2%). The most frequent immediate adverse effects were mild (40 infusions out of 955) in 22 cases, including: chills, flushing, fever, nausea and headache. Three patients experienced moderate effects (10 infusions out of 955) such as rash, severe headache, joint pain and chest tightness. None of the effects was anaphylactic type. It can be concluded that intravenous immunoglobulin is generally a well-tolerated medical agent for patients with antibody deficiency, but all patients should be monitored by a physician who is familiar with its indications, risks, adverse effects and their appropriate management.

Keywords: Intravenous immunoglobulins, Infusion, Adverse effects, Hypogammaglobulinemia.

INTRODUCTION

Immunoglobulin replacement therapy is an essential treatment in antibody deficiencies.[1,2] Failure to provide adequate replacement therapy results in mortality and long-term morbidity.[3,4,5,6] The first description of the antibody deficiency was that of Bruton, described in 1952, and the affected boy was treated with a human immunoglobulin preparation given subcutaneously.[7] Antibody replacement was subsequently administered intramuscularly until the 1980s, when intravenous immunoglobulin (IVIg) products were widely introduced. Since that time IVIg has become the most popular route of administration.[8]

The availability of IVIg in 1981 allowed a consider

Corresponding author: Dr. A. Aghamohammadi, Mailing address: Immunology, Asthma and Allergy Research Institute, Children's Medical Center, No. 62, Gharib St., Keshavarz Blvd. Tehran 14194, Iran, P.O.Box: 14185-863, Tel: +9821693 58 55, Fax: +98 21 642 89 95
E-mail: rezaei_nima@yahoo.com

ably high dose of IVIg to be administered, after which IgG level could already be normalized and taken under control. Several published comparative trials[9,10] documented the value of these higher dose, and indicated that high doses, of IVIg are associated with decreased frequency of infections.

Improved recognition of antibody deficiency has already resulted in the increased use of immunoglobulin replacement therapy.

IVIg administration is not without risk of adverse effects and complications, because IVIg is a biological product derived and purified from blood or plasma donation.[11]

Adverse effects of IVIg can be categorized into 3 types: immediate (those that occur during the infusion), delayed (those that occur hours to days after initiation of the infusion) and late adverse effects. The most common form being immediate adverse effects- that could be mild, moderate or severe.[2,12,13]

Mild adverse effects include: headache, flushing, chills, low back pain, muscle pains, nausea and fatigue. Moderate effects include: chest tightness, mild wheezing or vomiting. Severe effects manifested by severe breathlessness periods or wheezing, sensation of pressure in the chest plus other moderate symptoms persisting or rapidly getting worse, are extremely uncommon.[2,13]

The purpose of the present study is to determine the occurence of immediate adverse effects of intravenous immunoglobulin infusion in patients with antibody deficiency.

PATIENTS AND METHODS

The diagnosis of patients with antibody deficiency was made by the standard criteria of World Health Organization (8,14). During 36 months study (1997-2000), a total of 45 patients with antibody deficiency (30 males and 15 females) with the mean age of 14.2 ± 6.2 years (range: 2 to 32 years) were treated with IVIg (total 955 IVIg infusions).

All patients received human immunoglobulin, licensed for intravenous use, every 3-4 weeks at Children's Medical Center. The dosage of IVIg was 400-500 mg/kg every 3-4 weeks. Four types of IVIg preparations were used in our patients including: Sandoglobulin, Gamimmune-N, Nordimum and Intraglobulin F, all of which were purchased by the Ministry of Health and Medical Education of Iran.

Patients with antibody deficiency received IVIg in the Immunology and Allergy Department of Children's Medical Center (the referral center for primary immunodeficient patients). While receiving IVIg, all the patients were observed by a clinical immunologist and a nurse trained exclusively for IVIg therapy. Any adverse effect occuring was noted in the questionnaire, which was exclusively designed for this study.

RESULTS

Immunological diagnoses, established in these patients were Common variable immunodeficiency (13 male and 12 female patients) with the mean age of 15.8 ± 6.5 years, X-linked agammaglobulinemia (14 male patients) with the mean age of 10.9 ± 5.0 years, and IgG subclass deficiency (3 male and 3 female patients) with the mean age of 14.8 ± 5.3 years (Table I).

The mean of serum IgG level before and after IVIg therapy in all of patients was 256.2 ± 240.2 mg/dl and 680.3 ± 309.3 mg/dL, respectively. This difference was statistically significant (P-value < 0.001). The mean of IgG blood level significantly increased after IVIg therapy in Common variable immunodeficiency patients from 258.8 ± 162.0 mg/dl to 657.5 ± 262.6 mg/dl (P-value < 0.001), in X-linked agammaglobulinemia patients from 108.1 ± 98.6 mg/dl to 553.4 ± 157.3 mg/dl (P-value < 0.001), and in IgG subclass deficiency patients from 591.3 ± 400.4 mg/dl to 1071.7 ± 467.4 mg/dl (P-value = 0.002).

Among 955 infusions of intravenous immunoglobulin, 50 infusions (5.2%) were associated with adverse effects in 25 patients (28 of 745 injections in males and 22 of 210 injections in females) (Table I).

Mild adverse effects were observed in 4.2% of the 955 infusions (40 infusions), -in 22 out of the 45 patients- they comprised of chills, flushing, fever, nausea and headache (Table II,III). Occurrence of mild adverse effects in 15 out of 40 infusions was associated with rapid infusion, and in 3 out of 40 were associated with untreated infections. All of these symptoms subsided by slowing the rate of IVIg infusion.

Moderate adverse effects occurred in 1% of the 955 infusions (10 infusions) -in 3 out of the 45 patients- comprised of rash, severe headache, abdominal pain, joint pain, and chest tightness (Table II,III). Antihistamines and hydrocortisone were administrated for treatment of such adverse effects. As mentioned above, all adverse effects were categorized into mild and moderate groups and none of the effects were anaphylactic type.

DISCUSSION

In this study we determined the adverse effects of IVIg during immunoglobulin replacement therapy in 45 patients with parimay antibody deficiency. Out of 955 infusions of IVIg, 50 (5.2%) were associated with adverse effects (25 out of the 45 patients). The most immediate adverse effects were mild (40 out of the 955 infusions). Lee and his collegues[15] reported a 10% of adverse effects, noted in 13 cases. The most commonly

Table I. Demographic characteristics of 45 patients with primary antibody deficiency.

Patients No.	Sex	Age (year)	Disease	IgG (mg/dL)	IgM (mg/dL)	IgA (mg/dL)	IgG after IVIg (mg/dL)	Number of injections	Number of effects
1	Male	16	XLA	50	10	0	422	36	1
2	Male	13	XLA	170	0	0	540	34	2
3	Male	22	XLA	0	0	0	470	36	1
4	Male	9	XLA	240	29	0	620	23	0
5	Male	10	XLA	290	23	10	520	15	0
6	Male	15	XLA	203	26	6	800	36	0
7	Male	8	XLA	200	15	5	660	36	1
8	Male	2	XLA	180	44	16	840	5	0
9	Male	16	XLA	0	0	0	720	18	1
10	Male	9	XLA	50	30	10	580	13	0
11	Male	8	XLA	50	27	10	310	17	0
12	Male	9	XLA	0	0	0	425	24	0
13	Male	7	XLA	160	0	0	800	23	1
14	Male	8	XLA	50	10	5	320	16	0
15	Male	15	CVID	0	8	0	300	23	2
16	Male	9	CVID	50	228	7	1180	22	0
17	Female	26	CVID	290	65	58	720	16	1
18	Male	17	CVID	480	25	45	720	31	3
19	Female	17	CVID	200	0	0	450	26	3
20	Male	20	CVID	240	310	64	1300	26	0
21	Female	19	CVID	270	339	0	475	10	4
22	Female	10	CVID	340	320	10	470	6	2
23	Female	16	CVID	330	5	40	720	6	2
24	Female	16	CVID	50	12	10	250	12	0
25	Male	15	CVID	140	19	13	980	26	1
26	Male	11	CVID	380	110	26	480	27	1
27	Female	13	CVID	490	60	50	860	4	2
28	Female	4	CVID	300	20	12	460	12	0
29	Male	9	CVID	160	40	0	520	15	1
30	Female	12	CVID	340	182	47	820	14	0
31	Male	21	CVID	330	20	10	650	36	0
32	Female	15	CVID	520	115	52	540	7	0
33	Male	8	CVID	0	18	0	560	21	1
34	Male	32	CVID	110	50	0	550	30	2
35	Male	11	CVID	530	54	0	632	18	3
36	Female	20	CVID	310	380	0	720	36	5
37	Male	12	CVID	310	200	48	1100	27	1
38	Male	20	CVID	300	0	0	500	29	5
39	Female	28	CVID	0	0	0	480	16	3
40	Female	12	IgG Sd	250	80	42	820	16	0
41	Female	15	IgG Sd	400	40	15	520	14	0
42	Male	8	IgG Sd	820	58	62	1300	24	1
43	Female	24	IgG Sd	1128	245	235	1800	15	0
44	Male	14	IgG Sd	850	49	50	1250	31	0
45	Male	16	IgG Sd	100	55	0	740	27	0

XLA: X-linked agammaglobulinemia

CVID: Common variable immunodeficiency

IgG Sd: IgG subclass deficiency

Table II. Adverse effect observed during 955 IVIg infusions in 45 patients with primary antibody deficiency.

Score of effect	infusions		Patients	
	Number	Percent	Number	Percent
Mild	40	4.2%	22	48.9%
Moderate	10	1%	3	6.7%
Severe	0	0	0	0
Total	50	5.2%	25	55.6%

Table III. Types of effects during 955 IVIg infusions in 45 patients with primary antibody deficiency.

Type of effect	Affected number
Chills	40
Flushing	35
Fever	35
Nausea	30
Headache	28
Abdominal pain	10
Joint pain	3
Chest tightness	2

recorded side effects were headache and fever.

Bjorkander and his colleagues[16] determined the rate of adverese effects in 34 immunodeficient patients following 1040 infusions of IVIg therapy. Out of 1040 infusions, 49 infusions (4.7%) were associated with adverse effects, which were observed in 12 out of the 34 patients, and comprised of flushing, nausea and headache. In 4 cases, rapid infusion was associated with adverse effects.

In our study, occurrence of mild adverse effect in 15 out of 40 infusions with adverse effects was due to rapid infusion and they subsided after slowing the rate of infusion. These data show that mild adverse effects do not necessitate the cessation of the infusion, but the rate has to be slowed until the symptoms are subsided.

Sudden adverse effects during the treatment are almost always a result of an extremely rapid infusion rate,[17] thus controlling the infusion rate is very important in preventing adverse effects. The maximum safe rate is detemined by the patient's weight, therefore the infusion of IVIg should be started at an infusion rate of 0.01ml/kg/min for the first 30 minutes, gradually increasing to 0.07 ml/kg/min and not exceeding the maximum rate.[18]

In our study, 3 out of 40 cases with mild adverse effects were associated with untreated infections. The presence of active untreated bacterial infection is a contra indication to the IVIg infusion and the infusion has to be postponed until the infection is completely controlled by antibiotic therapy. If IVIg is infused in such circumstances it may lead to an immune complex formation, which can result in adverse effects.[15] It is therefore advisable to give antibiotic therapy for a two-day period, in order to control the infection before administrating the IVIg in such patients.

Moderate adverse effects were only noted in 1% of the 955 infusions, in 3 out of the 45 patients. These effects did not subside by slowing down the rate of IVIg infusion. The presence of moderate effects, such as chest tightness, mild wheezing or vomiting indicates that the infusions have to be discontinued. Antihistamines, aspirin, indomethacin or hydrocortisone may be used as a prophylaxis or treatment for such adverse effects.[2,18]

In another study (19) in which the levels of anti-IgA antibodies were measured in patients receiving IVIg (including these 3 formerly-mentioned patients), the

anti-IgA antibodies titer to total IgA ratios in these 3 patients were significantly higher, compared with other patients receiving IVIg.

Patients with primary antibody deficiencies may develop anti-IgA antibodies after infusion of blood, plasma or immunoglobulin containing IgA.[20,21,22,23] In a study by Burks, three patients with very high and rising titres of anti IgA antibodies were reported,[24] in whom life-threatening, anaphylactic reactions occurred after infusion of a few millilitres of immunoglobulin-containing IgA.

IgA-depleted preparations of intravenous gammaglobulin should be used for patients with very high or rising titres of anti- IgA antibodies.[25,26]

As we observed in our study, the anaphylactoid effects are extremely rare.[27]

CONCLUSION

From the results it is concluded that the intravenous immunoglobulin (IVIg) therapy is a well-tolerated method of treatment for patients with antibody deficiency. The main causes of an adverse effects, following IVIg therapy are: rapid infusion, the presence of active untreated bacterial infection in patients on the day of infusion and the presence of anti-IgA antibodies. In order to prevent the occurrence of immediate adverse effects during infusion, it is therefore important to ensure that the patient is not unwell prior to infusion, so over active infections on the day of infusion must be excluded by taking immediate history and physical examination. Finally it can be recommended that the titer of anti-IgA must be checked in any patient with antibody deficiency who is planned to be on regular IVIg therapy.

ACKNOWLEDGEMENTS

We are grateful to the laboratory personnel Mrs. A. Isaeian, Mrs. L. Nikfarjam, Mrs. A. Azimdoust and to our secretariate personnel Mrs. M. Andali, Miss H. Eghdami, Mrs. Sh. Ekrami, Miss. N. Hasani, and Miss. Z. Shobayri for their arrangements and administrative efforts.

REFERENCES

1. Cunningham-Rundles C, Siegal FP, Smithwick EM, Lion-Boule A, Cunningham-Rundles S, O'Malley J, et al. Efficacy of intravenous immunoglobulin in primary immunodeficiency disease. Ann Intern Med. 101: 345-9, 1984.
2. Aghamohammadi A. Immunoglobulin Replacement Therapy. In Farhoudi A: Immunodeficiency Disorders In Iran. Shayan Nemoodar Company, Tehran, pp. 67-78, 2002.
3. Blore J. Haeney M. Primary antibody deficiency and diagnostic delay. BMJ. 298: 516-7, 1989.
4. Hermaszewskki RA, Webster ABD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. Q J Med; 86: 31-42, 1993.
5. Aghamohammadi A, Moin M, Farhoudi A, Pourpak Z, Movahedi M, Rezaei N, et al. The clinical spectrum of respiratory diseases in patients with primary antibody deficiencies; a clinical survey of patients from Iranian Primary Immunodeficiency Registry. Iranian Journal of Allergy, Asthma and Immunology. 1: 135-140, 2002.
6. Aghamohammadi A, Jalali F, Farhoudi A, Pourpak Z, Rezaei N, Khazali Sh, Hosseini Nik H. Ear, Nose, and Throat manifestations in patients with primary antibody deficiencies. Acta Medica Iranica. 39: 164-8, 2001.
7. Bruton OC. Agammaglobulinaemias. Pediatrics 9: 722-727, 1952.
8. Primary immunodeficiency diseases. report of a WHO scientific group. Clin Exp Immunol 109: S1-28, 1997.
9. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. Lancet i: 1075, 1987.
10. Liese JG, Wintergerst U, Tympner KD, Belohardsky BH. High -vs. low-dose immunoglobulin therapy in the long-term treatment of X-linked agammaglobulinemia. Am J.Dis Child; 146(3): 335-9, 1992.
11. Ballow M. Intravenous Immunoglobulins. Clinical experience and viral safety. J Am Pharm Assoc; 42: 449-59, 2002.
12. Misbah S, Chapel H. Adverse effects of immunoglobulin therapy. Drug Safety; 9: 254-62, 1993.
13. Haeney M. Intravenous immunoglobulin in primary immunodeficiency. Clin Exp Immunol; 97 Suppl 1: 11-5, 1994.
14. Aghamohammadi A, Moin M, Farhouidi A, Pourpak Z, Rezaei N, Abolmaali K, Movahei, et al. Primary immunodeficiency in Iran; First report of the national registry of PID in children and adults. J Clin Immunol. 22: 375-80, 2002.
15. Lee YC, Woodfield DG, Douglas R. Clinical usage of intravenous immunoglobulins in Auckland. N Z Med J 111: 48-50, 1998.
16. Bjorkander J, Wadsworth C, Hanson LA. 1040 prophylactic infusions with an unmodified intravenous immunoglobulin product causing few side effects in patients with antibody deficiency syndromes. Infection 13: 102-10, 1985.
17. Bagdasarian A, Tonetta S, Harel W, Mamidi R, Uemura Y. IVIG adverse reactions: potential role of cytokines and vasoactive substances. Vox Sang 74: 74-82, 1998.
18. Cunnigham-Rundles C. Immunoglobulin treatment in immunodeficiency diseases. In Rich R.R. Clinical Immunology, Principles and practice, Mosby. England pp. 103-11, 2001.

19. Roohi R, Aghamohammadi A, Shokri F. Association between anti-IgA antibody and development of adverse reaction in immunodeficient patients under immunoglobilin therapy. Irn J Med Sci 26: 90-4, 2001.
20. Bjorkander, J, Hammarstrom L, Smith CIE, Buckley RH, Cunningham-Rundles C, Hanson LA. Immunoglobulin prophylaxis in patients with antibody deficiency syndromes and anti-IgA antibodies. J Clin Immunol; 7:8-15, 1987.
21. Frankel SJ, Polmar SH, Grumet FC, Wedner HJ. Anti-IgA antibody associated reactions to intravenous gammaglobulin in a patient who tolerated intramuscular gammaglobulin. Ann Allergy 56: 436-9, 1986.
22. Ferreira A, Garcia Rodriguez MC, Lopez-Trascasa M, Pascual Salcedo D, Fontan G. Anti-IgA antibodies in selective IgA deficiency and in primary immunodeficient patients treated with gamma-globulin.Clin Immunol Immunopathol 47: 199-207, 1988.
23. Ferreira A, Garcia Rodriguez MC, Fontan G. Follow-up of anti-IgA antibodies in primary immunodeficient patients treated with gamma globulin. Vox Sang 56: 218-22, 1989.
24. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions following gammaglobulin administration in patients with hypogammaglobulinaemia. N Engl J Med; 314:560-4, 1986.
25. Cunningham-Rundles C, Wong S, Bjorkander J, Hanson LA. Use of an IgA-depleted intravenous immunoglobulin in a patient with an anti-IgA antibody. Clin Immunol Immunopathol Feb; 38: 141-9, 1986.
26. Cunningham-Rundles C, Zhou Z, Mankarious S, Courter S. Long-term use of IgA-depleted intravenous immunoglobulin in immunodeficient subjects with anti-IgA antibodies. J Clin Immunol Jul; 13: 272-8, 1993.
27. Haeney M. Intravenous immunoglobulin in primary immunodeficiency. Clin Exp Immunol Jul; 97 Suppl 1: 11-15, 1994.