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Adverse reactions to intravenous immunoglobulin therapy

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ABSTRACT

The intravenous immunoglobulin (IVIG) therapy in Pediatrics has very specific indications. In some of these, like primary immunodeficiencies, it is a long term therapy. Although the adverse events (AE) are not so common (only 5%), they are very important issues when they appear. The adverse events can be immediate or delayed. We present our experience regarding the adverse events in fourteen patients who received IVIG in the last four years, from 2004 to 2007. As risk factors, we incriminated high rate of perfusion and preformed antiIgA antibodies. The risk factors for adverse events in IVIG treatment should be known by the pediatricians in order to prevent such reactions.

BACKGROUND

The principal uses of intravenous immunoglobulin (IVIG) in pediatric patients are ***replacement therapy in immunodeficiency*** and ***immunomodulatory therapy in autoimmune*** and ***inflammatory conditions*** such as immune thrombocytopenic purpura and Kawasaki disease. IVIG therapy is currently approved to treat six conditions: primary immunodeficiencies, immune mediated thrombocytopenia, Kawasaki syndrome, recent bone marrow transplantation, chronic B-cell lymphocytic leukemia, pediatric HIV-1 infection (1-5). Clearly, the great majority of these conditions belong to the pediatric field.

IVIG is usually well tolerated, with adverse events (AE) occurring in less than 5% of the cases (6, 7). There are studies about AE in IVIG products usage and in one of these studies the percentage for AE was of 0.35% (8). These complications are generally believed to be allergic reactions consisting of vasomotor symptoms. AE following intravenous immunoglobulin infusions occur during the infusion itself (immediate AE) and after the infusion has ceased (delayed AE) infusion. ***"The risks involved fall into two main categories: those associated with the infusion of intravenous immunoglobulin and the longer term risks of blood born viruses or currently unknown organisms"*** (9). The immediate AE represent a percent of 10.3% but the delayed AE (41.4%) are more important. The last category noticed AE between 24-48 hr or 48-72 hr or 76-96 hr (7days) and it is six times more frequent than immediate reaction per patient, four times more

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Adverse events
I Respiratory
Apnea
Adult Respiratory Distress Syndrome (ARDS)
Transfusion – Related Acute Lung Injury (TRALI)
Cyanosis
Hypoxemia
Pulmonary edema
Dyspnea
Bronchospasm
II Cardiovascular
Cardiac arrest
Thromboembolism
Vascular collapse
Hypotension
III Neurological
Coma
Loss of consciousness
Seizures
Tremor
IV Integumentary
Stevens-Johnson syndrome
Epidermolysis
Erythema multiform
Bullous dermatitis
V Hematologic
Pancytopenia
Leucopenia
VI Hemolysis
Positive direct antiglobulin test (Coombs)
VII General Body as a Whole
Pyrexia
Rigor
VIII Musculoskeletal
Back pain
IX Gastrointestinal
Hepatic dysfunction
Abdominal pain

TABLE 1. Adverse events for IVIG administration

Risk factors for AE:
Patient age
Underlying condition
Dose
Concentration
IgA content
Stabilizing agent
Rate of infusion

TABLE 2. Risk factors for AE

frequent per infusion. Delayed headache is the most common AE in this subgroup having a significant morbidity with impact on the child's daily activities. AE, especially headache, are less likely rate dependent as previous studies have suggested (10).

IVIG is derived from pooled ***donor serum*** by ***ethanol fractionation*** with ***additional steps to remove immunoglobulin aggregates***. Preparations are then ***stabilized*** using substances such ***as human albumin, glycine, polyethylene glycol,*** or ***sugar*** (sucrose, maltose, or glucose)**.** As a result of fractionation and addition of stabilizers, ***reactions may occur to either immunoglobulin aggregates or to stabilizing agent***. The formation of IgG aggregates during IVIG manufacture or storage is believed to cause these reactions. To prevent aggregate formation, purified IgG is stabilized with various carbohydrates such as those already mentioned above (sucrose, maltose, glucose) and sorbitol, or other substances such as human albumin and glycine. Procedures that remove or minimize immunoglobulin aggregation reduced the immediate adverse reactions rate in children by approximately nine fold.

Despite all these methods to reduce adverse reactions, IVIG infusions are associated with the following AE: fever, flushing, chills, headache, pain at the infusion site, vertigo, fatigue, nausea, abdominal pain, myalgia, rash, arthralgia, low back pain, malaise, renal failure, aseptic meningitis syndrome, hemolytic anemia, anaphylaxis, tachycardia, palpitation, hypotension, bronchospasm (wheezing), thrombotic complications, cutaneous vasculitis (in type II mixed cryoglobulinemia), eczematous dermatitis and alopecia, complement consumption associated with an eczematous cutaneous reaction, life-threatening human parvovirus B19 infection and hepatitis C (11-15). These AE are listed in the **Table 1** (16) and the risk factors for AE (16) are listed in **Table 2**.

The major life-threatening adverse reactions are aseptic meningitis, hemolytic anemia, renal dysfunction, anaphylaxis and thrombotic complications. ❑

ASEPTIC MENINGITIS SYNDROME

Has a high rate (11%) within the first 24 hours after infusion, by IgG penetration into the cerebrospinal fluid (CSF). Investigation of the CSF shows pleocytosis, eosinophilia, and IgG elevation. The symptoms (severe headache, meningismus, photophobia, and fever) last 3-5 days. Risk factors for this syndrome are the ***history of migraine*** (the cerebrovascular sensitivity that it is not related to the type of preparation or infusion rate), IgG itself, stabilizing products, cytokine release triggered by IVIG. Within several days after discontinuation of treatment, remission appears without sequelae (17,18). ❑

ACUTE RENAL FAILURE

Exogenous immunoglobulins can cause renal injury by a mechanism unrelated to the IG (19) (as seen in renal injury by endogenous immunoglobulins). The renal biopsy shows acute tubule necrosis, marked vacuolization and edema of the proximal tubules *without immunoglobulin deposition*; proximal tubular cell swelling are identical with those seen in biopsy specimens from patients with severe hypokaliemia, contrast induced nephropathy, cyclosporine toxicity and following IV administration of carbohydrates (glucose, manitol, dextran and sucrose). When given IV, sucrose is filtered at the glomerulus and excreted virtually unchanged. *The vast majority of IVIG inducing acute tubule necrosis and renal failure* are IVIG preparations that contain *sucrose* stabilizers. In USA, Sandoglobulin and Panglobulin contain 1,7g sucrose per gram of IgG and Gammar-P IV contains 1g/gram of IgG. Between 1985 and 1999 these products accounted for 90% of all reported cases of IVIG induced acute renal failure. Other products inducing renal adverse events are those containing maltose or glycine stabilizers.

The products stabilized with sorbitol, albumin or glucose have not been reported to cause renal adverse reactions.

An **immunologic response** may also be the cause of IVIG associated renal failure (a case of a lymphoma producing IgM kappa paraproteins with severe mixed cryoglobulinemic nephropathy and immunostaining strongly positive for IgM and IgG light chain deposition in the glomerular capillaries and subendothelial sites). The presence of rheumatoid factor proteins in these deposits was established (20).

To prevent acute renal failure precautions should be taken: the assurence that the patient is not volume depleted, the absence of risk factors for renal complications (pre-existing renal disease, diabetes, nefrotoxic agents, paraproteinemia), the control of renal function (BUN/serum creatinine) prior to initial infusion, and than again at appropriate intervals thereafter. The IGIV products must be properly diluted (250-350mOsm/L) and must be given at the right infusion rate (maximum rate = 0,07ml/Kg/hour). ❑

HEMOLYSIS

IVIG products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with IG causing a positive direct antiglobulin reaction, and, rarely, hemolysis. IVIG may also enhance RBC sequestration. ❑

ANAPHYLAXIS

IVIG can induce reactions in patients with immunoglobulin A (IgA) deficiency; this PID appears with a frequency of 1/1000-1/500 people. Serious anaphylactoid reactions occur soon after the administration of IVIG. Anaphylaxis associated with sensitization to IgA in patients with IgA deficiency can be prevented by using IgA-depleted immunoglobulin products. On the other hand, presence of IgG class anti-IgA antibodies is not always associated with severe adverse reactions (21). ❑

THROMBOSIS

IVIG is associated with rare cases of thrombosis. It was cited to cause disseminated intravascular coagulation, transient serum sickness**,** and transient neutropenia. Underlying risk factors are thrombophilia, hypercholesterolemia, high sodium content, factor XI content, rapid infusion rate, deep venous thrombosis, history of vascular disease and stroke, atrial fibrillation, arterial hypertension, hepatic veno-occlusive disease, previous bone marrow transplantation. The reported thrombotic events have developed in vessels distal from the infusion sites. Most of these events developed during or immediately after IVIG infusion. The pathogenesis mechanisms are IVIG-induced platelet activation, IVIG dose-dependent increased plasma viscosity – for 5 days after treatment (post infusion hyperproteinemia, pseudohyponatremia) and contamination of IVIG preparations by coagulation factor XI. Precautions like slower rate of infusion (8-12 hours), avoiding high-dose infusion (400-1000 mg/Kg/day), avoiding blood products given concomitantly with IVIG, searching for acquired or inherited thrombophilia, cryoglobulins or monoclonal gammapathies, represent tools for preventing thrombotic events (22-24). ❑

TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)

Patients treated with IVIG may develop noncardiogenic pulmonary edema (TRALI),

	Humaglobin	Octagam	Endobulin	Isiven
Sodium content				
IgG	–	–	–	–
Albumin	95%	>99%	>95%	95%
Glycine (mg/ml)	–	–	–	–
Glucose	15	–	Macrogol	–
pH	15	Maltose, 100	+	+
IgA (mg/ml)	50	trace	50	50

TABLE 3. Comparison of the composition of the IVIG products used in IOMC patients

No	ID	Age (y)	DGN	No infusions
1	BMC	21	XLA	50
2	PCF	12	XLA	49
3	MLC	12	CVID	54
4	SF	17	WAS vs XLA	14 (+50)
5	BAI	16 1/2	AT	36 (+64)
6	GAG	3	XLA possible	3
7	CA	2	SCID (PNP)	2
8	SD	7	Hypogammaglobulinemia	2
9	CB	2	Central cell deficiency	2
10-14			Kawasaki disease (2 g/kg)	5
			TOTAL	217

TABLE 4. IVIG infusions with immunoglobulins in our patients
Legend: ID, identity; y, years; DGN diagnosis; XLA, X linkated agammaglogulinemy; CVID, common variable immunodeficiency; WAS, Wiskott-Aldrich syndrome; AT, Ataxia-Telangiectasia syndrome; SCID (PNP), severe combined immunodeficiency, Central cellular deficiency (CD3+<NK>) +CD19+ < +HypoIgG

characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function and fever, which typically occur within 1-6 hours after transfusion (necessitating oxygen therapy with adequate ventilator support). In suspected cases, anti-neutrophil antibodies must be searched for both in the product, and in the patient's serum (25). ❑

MATERIAL AND METHODS

We present our experience in IVIG use in last four years, 2004-2007, in respect to the adverse events. In the Institute for Mother and Child Care, Bucharest, in the selected period, fourteen patients were treated with IVIG. ❑

OUTCOMES

There were used four different IVIG preparations: Humaglobin (Teva), Octagam (Farmexim), Endobulin (Baxter), Isiven (Kedrion Spa). Some differences between these products are illustrated in **Table 3** (11).

We gave a dose of IVIG of 400mg/Kg every 28 days, using a peripheral line. Patients were pre-medicated with IV steroids (Hydrocortisonum hemisuccinatum or Dexamethasonum or Methyl-Prednisolonum).

In this period, our 14 patients summarized 217 IVIG infusions (**Table 4**).

The rules for administering the IVIG must be respected: IVIG should reach room temperature before infusion. Controlled infusion devices are recommended.

The rate of infusions is different for the first infusion and for the following ones:

- 15 minutes: 30 ml/hr
- 15 minutes: 60 ml/hr
- 15 minutes: 90 ml/hr
- 30 minutes: 120 ml/hr
- then: 250 ml/hr

For subsequent infusions the rate varies from 60 ml/hr to 250 ml/hr. Some patients tolerate rapid infusions.

Temperature, pulse and BP must be measured at the beginning of IVIG and during the infusion (if necessary). In long time administrations, the medical necessity of IVIG should be reevaluated one year after initiating therapy and every two years thereafter, by reassessment

of immune response to protein and polysaccharide antigens.

All our AE in cases of PID were *immediate reactions*. We didn't notice delayed reactions because our patients leave the hospital 24 hours after the start of therapy (in the immunodeficiency cases). We use to warn parents about the delayed reactions possibility but they didn't report such events. No delayed reactions were noted in the Kawasaki patients.

Immediate adverse events in our patients (**Table 5**) were general (malaise, pallor), cardiovascular (tachycardia, cold extremities, arterial hypotension), neurological (psychomotor agitation), chills, lumbar violent pains, respiratory (cough, wheezing), hematological (eosinophilia). We have a suspicion of neurodegenerative disease linked to IVIG in one case. In this case, CEMA (meningoencephalitis caused by enteroviruses) was eliminated based on negative tests for Enteroviruses. In one case we found an unusual association between the XLA syndrome and a chronic arthritis, with recurrent episodes (**Table 6**).

We have encountered two extremes among our patients, concerning the tollerated infusion rate:

a) high-infusion rate tolerant (BMC, 21 yrs old: 20 grams of IVIG in 2 hr!);
b) slow-infusion rate tolerant (MLC, 12yrs old: 10 grams of IVIG in 8 hr). ❑

No	Name	Age (years)	Diagnosis	Adverse events	No events	Immunoglobulin	Risk factor incriminated
1	MCL	12	CVID	Lumbar violent pains Chills Psychomotor agitation Tachycardia Cold extremities	3	Isiven Endobulin Humaglobin	High infusion rate
2	BAI	16	AT (IgA: 0)	Malaise Chills Cough Wheezing Cold extremities Arterial hypotension Palor Eosinophilia	No events	Isiven Endobulin Humaglobin Octagam – "traces" IgA	Antibodies to IgA
3	SF	17	WAS vs XLA	Neurodegenerative disease	After 13 years of IVIG treatment		

TABLE 5. Adverse events in IVIG administration in our patients

No	Name	Age (years)	Diagnosis	Associated disease
4	PCF	12	XLA	Chronic arthritis (right knee – recurrent episodes). The presence of ragocytes and inflammatory cells in the synovial fluid permits to establish the diagnosis of oligoarthritis/JIA as likely rare associated disease, but ***not an adverse event of IVIG.***

TABEL 6. Unusual association between XLA syndrome and chronic arthritis

Conclusion

1. From the multitude of adverse reactions to IVIG treatment we met only immediate events.
2. The most severe adverse events (life threatening) are: aseptic meningitis, acute renal failure, anaphylactic reactions, thrombosis, and hemolytic anemia.
3. Awareness of the risk factors for these adverse events is mandatory among Pediatricians.
4. Fortunately, at this moment, in our country, IVIG products containing sucrose as stabilizer agent are unavailable and this is a possible explanation for the absence of IVIG related renal disease in our patients.
5. Risk factors identified in our group of patients were high infusion rate and high content of IgA.
6. The neurodegenerative disease (demyelinating type) remains to be confirmed as a possible complication of the long time treatment with IVIG.

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