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ORIGINAL ARTICLE

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Metabolic and hematologic changes occurring after rapid intravenous infusion of gammaglobulin in patients with antibody deficiency syndromes

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Objective: We wished to investigate whether increased IgG infusion rates are associated with metabolic and hematologic changes in pediatric patients with antibody deficiency syndromes. **Methods:** We studied 7 patients (2-16 years old) with primary antibody deficiencies who had been on regular IgG replacement treatment, 350-600 mg/kg/dose every 3 weeks with a 3% IVIG preparation, for periods ranging from 6 months to 4 years. Initially, the IgG concentration of IVIG preparations was increased to 6, 9 and 12% in consecutive infusions at a constant IgG infusion rate of 4 mg/kg/min. Subsequently, the infusion rates were increased to 8, 12, and 16 mg/kg/min using the IVIG 12% preparation. **Results:** Clinically, all patients tolerated increases in IVIG concentrations while the infusion rate was 4 mg/kg/min. However, 3 patients presented side effects when the infusion rate was increased to 8 and 16 mg/kg/min. **Conclusion:** We conclude that metabolic and hematologic sides effects occur with rapid infusion of IVIG even in patients who tolerate the increased infusion rate clinically. The advantages of using high infusion rates have to be re-evaluated.

Uniterms: Intravenous immunoglobulin. Immunodeficiency. Side effects. Infusion rates. Leukopenia.

INTRODUCTION

Intravenously-infused immunoglobulins (IVIG) have been successfully used for IgG replacement treatment in patients with primary and secondary antibody deficiencies (AD) and in patients with certain inflammatory and autoimmune diseases.[1-4] Adverse events associated with the administration of IVIG preparations with IgG concentrations ranging from 3 to 6% have been reported in only 1 to 15% of patients (usually in less than 5%).[5,6] Most of the reactions described were mild and self-limited. Vasomotor symptoms include chills, fever, flushing, headache, nausea, rise in temperature, vomiting and malaise. They can probably be related to anti-complementary activity of aggregated gammaglobulin.[7] Recommended infusion rates, expressed as volume of IVIG per patient weight for 3-6% IVIG preparations, were 0.01-0.02 ml/kg/min initially, increasing up to a maximum rate of 0.1 ml/kg/min.[2] These infusion volumes correspond to IgG infusion rates of 0.3 to 6 mg/kg/min.

Recently, more concentrated preparations with 10-12% IgG have become available for clinical use, leading to considerably higher IgG infusion rates. Schiff et al. administered 12% IVIG to 16 patients with AD at increasing IgG infusion rates, up to a maximum of 30.6

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mg/kg/min.[8] Eight patients tolerated infusion rates higher than 10 mg/kg/min without adverse reactions, but only 5 tolerated a rate higher than 20 mg/kg/min. The observed side effects were agitation, irritability, back pain, fever, nausea, cold, vomiting and chills in eight patients. Laboratory analyses were not reported.

In IVIG preparations with higher concentrations of IgG, other pharmacologic properties like osmolarity and pH are also changed.

The aim of this study was to investigate whether increasing IgG concentrations and infusion rates would induce acute metabolic and hematologic changes even when the increases were well-tolerated clinically.

METHODS

Patient population

Patient diagnoses and doses of IgG per infusion are summarized in Table 1. All patients had been on regular IgG replacement treatment, 300-400 mg/kg every 3 weeks with a 3% IVIG preparation for periods ranging from 6 months to 4 years. In one patient, the dose was increased to 600 mg/kg because of infection occurring at lower IgG doses.

All patients had received 3% IVIG (Sandoglobulin›, Sandoz, Switzerland) for at least 6 months without any adverse reactions prior to entering the study.

All patients had normal levels of urea, creatinine, oxaloacetic and pyruvic transaminases, and normal blood counts before entering the study.

This study was approved by the ethical committee of the Universidade Federal de São Paulo, Escola Paulista de Medicina, and informed consent was obtained from the parents of all patients.

Study design

For our study, one IVIG product (Sandoglobulin®, Sandoz, Switzerland - diluted in saline 0.9%), prepared with acid treatment at pH 4.0, was used in all patients. The pH and osmolarity in the final preparations changed with increasing concentrations of IgG: 3%: pH = 6.58 and 498 mOsm/l; 6% pH = 6.61 and 690 mOsm/l; 9%: pH = 6.64 and 882 mOsm/l; 12%: pH = 6.8 and 1074 mOsm/l.

During the first phase of the study, we maintained a constant infusion rate of 4 mg/kg/min with the aid of an infusion pump (Santronic›, São Paulo, Brazil) and increased the IVIG concentration to 6, 9 and 12% respectively at each new infusion. When a flow rate of 4 mg/kg/min was reached at the 12% concentration without any side effects, we performed the second phase of the study. In this phase, the IgG concentration of 12% was maintained and the rate of infusion was increased at each new infusion to 8, 12 and 16 mg/kg/min, respectively. The rate of infusion was increased only if the patients did not present side effects in the previous infusion.

Patients were monitored clinically before, during and at the end of each infusion.

Plasma osmolarity and venous blood gases were measured before and immediately after the end of each infusion throughout the study. When the infusion rate was increased above 4 mg/kg/min, an additional blood sample was obtained 30 minutes after completing the infusion. Blood-cell counts were performed before and after infusion only when the concentration of 12% IVIG was reached.

Pre-infusion samples were obtained immediately prior to IVIG administration. After completing the IVIG infusion, the IV line was kept open with a saline solution. Five to 10 minutes later, post-infusion samples were obtained after eliminating the first 3 ml of blood to avoid contamination with saline. A second post-infusion sample was obtained 30 minutes after complete IVIG

Table 1
Patient population: diagnosis and dose of IVIG/kg

Patients	Age (years)	Immunodeficiency	Dose/mg/kg	Length of treatment before study (months)
1	7	XLA*	400	18
2	5	XLA	350	48
3	5	XLA	400	18
4	11	CVI*	600	36
5	16	CVI	300	48
6	4	IgG2 D*	400	6
7	3	IgG2 D	400	6

*XLA = X-linked agammaglobulinemia; CVI = common variable immunodeficiency; IgG2 D = IgG2 deficiency

administration, for the determination of blood gases only. All tests were done in the same laboratory.

Statistical analysis

Results obtained before and after IVIG infusions were compared using the paired Student's *t* test. Results obtained before, and 5 and 30 minutes after the end of the infusion were compared using analysis of variance (ANOVA). Comparison of results of sequential infusions with increasing rates were performed using ANOVA for repeated measurements. P values are only indicated when lower than 0.05.

RESULTS

Clinically, all seven patients tolerated the first phase of the study, which tested increasing IgG concentrations from 6 to 12% while maintaining a constant IgG infusion rate of 4 mg/kg/min. In the second phase, when the infusion rates were increased, some side effects were observed: one patient presented abdominal pain and vomiting at an infusion rate of 8 mg/kg/min and, when the infusion rate was increased to 16 mg/kg/min, 2 additional patients developed side effects. One complained of abdominal pain during infusion, and the other, after the infusion had headache without vomiting, which persisted for several hours while at his home, with spontaneous remission. Therefore, lumbar puncture was not considered necessary. Four patients tolerated an infusion rate of 16 mg/kg/min without any complaints. No patient had significant changes in vital signs pre- and post-infusion.

There was a trend towards higher osmolarity after completion of the IVIG infusion at most IVIG concentrations and infusion rates tested (Table 2). The percentage of increase was higher with 12% IgG than with lower IgG concentrations. However, the increase in osmolarity was not observed at the highest infusion rate of 16 mg/kg/min. None of the changes in osmolarity reached significance and all values were within the normal range for our laboratory .

The values of blood gases before and 5 minutes after IVIG infusion for different gammaglobulin concentrations and using different IgG infusion rates did not show any significant difference. However, there were significant changes in pCO_2, HCO_3, CO_2 and base excess (BE) without changes in pH, pO_2 and O_2 saturation 30 minutes after the end of the infusion at a flow rate of 16 mg/kg/min (Table 3).

There was a small, but significant, hemodilution effect 5 min after infusion rates of both 4-8 and 16 mg/kg/min of the 12% IVIG solution as shown by a decrease in red-cell count, hematocrit and hemoglobin levels (Table 4). There was no difference in the hemodilution effect between the 2 infusion rates. The percentage post-IVIG

Table 2
Mean plasma osmolarity (mOsm/l) of children with primary antibody deficiency before and after different schedules of IVIG infusion

IVIG Concentration (%)	6	9	12	12	12	12
Infusion Rate (mg/kg/min)	4	4	4	8	12	16
Osmolarity (mOsm/l)						
Before	281	277	285	282	284	283
After	289	286	302	296	302	282
% increase	2.8	3.2	5.9	4.9	6.3	-3.5

Table 3
Venous blood gases before and after (5 and 30 minutes) 12% IVIG at infusion rate 16 mg/kg/min (N=4)

	Before*	5 minutes*	30 minutes*	P value
pH	7.36 (0.04)	7.35 (0.18)	7.36 (0.20)	NS
pCO_2	35.7 (5.28)	33.5 (1.85)	22.2 (4.63)	0.01
pO_2	65.7 (16.92)	82.7 (8.31)	85.4 (13.06)	NS
HCO_3	20.12 (1.35)	18.77 (1.14)	12.6 (2.18)	0.003
CO_{2t}	21.22 (1.54)	19.85 (1.17)	13.32 (2.34)	0.004
BE	-4.25 (0.55)	-5.6 (1.16)	-11.55 (2.02)	0.001
$SatO_2$	89.6 (6.92)	95.22 (1.28)	95.9 (3.03)	NS

* Mean (SD)

infusion decrease was higher in white cells than in red cells and the effect increased with increasing IgG infusion rates (Table 4). The range of the decreases was 32 to 82% at a flow rate of 4-8 mg/kg/min and 44 to 90% at a flow rate of 16 mg/kg/min. Monocytes had the highest percentage decrease in comparison to other white cells at flow rates of both 4-8 and 16 mg/kg/min. The percentage neutrophil decrease was lower at a flow rate of 4-8 than at 16 mg/kg/min (32% and 60% decrease, respectively). Platelet numbers were also decreased after infusion, but to a lesser degree than the white cells. The percentage decrease was 21.5% at infusion rates of 4-8 mg/kg/min and 31.2% at 16 mg/kg/min (Table 4).

DISCUSSION

Side effects such as chills, fever, flushing, headache, nausea, increased temperature, vomiting and malaise are considered mild adverse reactions of IVIG infusion. They are often associated with an increased IgG infusion rate and usually improve rapidly when the infusion rate is lowered.[9] These reactions have been attributed to antigen-antibody reactions or to possible contaminants or even stabilizers that may have been used during the manufacturing process.[5] The clinical side effects we observed in 2 of our patients were mild and responsive to infusion-rate reduction (IVIG 12% - 8 and 16 mg/kg/min).

In a third patient, we observed a persistent headache, which remitted spontaneously after 12 hours (IVIG 12% - 16 mg/kg/min). Acute aseptic meningitis has been reported as a cause of recurrent IVIG-associated headaches.[10] Analysis of cerebrospinal fluid has revealed neutrophilic pleocytosis with normal or mildly raised protein levels.[5,9] Whether or not the transient headache seen in our patient was a mild form of aseptic meningitis could not be determined since the performance of a lumbar puncture was not clinically justifiable. In accordance with the study by Camp-Sorrell et al. which showed a weak correlation between vital signs during IVIG administration and adverse reactions,[11] we did not observe significant changes in vital signs in our patients who developed side effects.

The osmolarity of IVIG solutions increases with increasing IgG concentrations. In addition to IgG, the IVIG preparations utilized in this study contains 5-10% sucrose; the diluent is sodium chloride. We observed a trend to higher plasma osmolarity in all patients regardless of clinical side effects, even at flow rates of 4 mg/kg/min. The percentage of increase in osmolarity was higher with the 12% IVIG preparations, independent of the flow rates. No increase in osmolarity was observed with infusion rates of 16 mg/kg/min, which may be due to the short infusion time. We do not know whether, after longer periods of time, e.g. 30 minutes after the end of infusion, we would also have detected changes in plasma osmolarity at this high flow rate. Some commercial IVIG preparations use albumin and sugar as additives. Based on our results with one IVIG preparation, we suggest that further studies should evaluate changes in osmolarity caused by other IVIG preparations too.

Blood viscosity after IVIG infusion increases proportionally to the IgG concentration in the preparation used and may still be elevated 3 to 5 days after IVIG infusion.[12] The authors of this finding postulated that changes in viscosity occurring after IVIG therapy could impair blood flow and increase the risk of myocardial infarction or stroke in patients at risk from cardiovascular and thromboembolic events. Side effects of IVIG infusion, such as acute renal failure[13] and thromboembolic events[14] may be associated with increasing plasma viscosity. Therefore, increased plasma viscosity could represent an

Table 4
Blood cells count before and after Sandoglobulin® 12% infusion (5 minutes) at different flow rates

	IgG infusion rate: 4-8 mg/kg/min (N=5)				IgG infusion rate: 16 mg/kg/min (N=4)			
	Before*	After*	%decrease	P value	Before*	After*	%decrease	P value
Red cells (x10^6/mm^3)	4.44 (0.05)	4.02 (0.29)	9.4%	0.02	4.35 (0.28)	3.97 (0.15)	8.7%	NS
Hematocrit (%)	36 (1.58)	32 (1.64)	11.1%	0.009	35 (2.88)	32 (0.95)	8.5%	0.03
Hemoglobin (g/dl)	11.7 (0.39)	10.5 (0.93)	10.25%	0.05	11.3 (0.37)	10.2 (0.20)	9.7%	0.05
White cells (cells/mm^3)	9400 (3276)	5960 (1903)	36.6%	NS	8625 (4073)	3450 (1112)	60%	0.04
Neutrophils (cells/mm^3)	6873 (2739)	4658 (966)	32.2%	NS	8625 (2036)	3450 (556)	60%	0.04
Eosinophils (cells/mm^3)	247 (221)	134 (95)	45.7%	NS	242 (270)	103 (64)	57.4%	NS
Lymphocytes (cells/mm^3)	3480 (1530)	2058 (790)	40.8%	0.02	3396 (1743)	1895 (628)	44.2%	NS
Monocytes (cells/mm^3)	515 (247)	93 (68)	81.9%	0.02	658 (329)	62 (42)	90.5%	0.03
Platelets (x10^3)	331 (32)	260 (56)	21.5%	0.03	320 (118)	220 (60)	31.2%	0.04

* Mean (SD)

additional risk for elderly patients and for HIV-infected patients with hypergammaglobulinemia who receive large amounts of IVIG. The relationship between changes in osmolarity observed in our patients and the reported changes in viscosity is unclear at this time. Further studies of both changes need to be performed in parallel studies in the same patients.

The pH of Sandoglobulin® is similar for all IgG concentrations used and is comparable to that of other commercial IVIG preparations,[15] but it is lower than that of the human body pH. None of our patients presented significant changes in blood pH, but 30 minutes after infusion, they showed metabolic acidosis (base excess consumption and fall in HCO_3) compensated by hyperventilation (fall in pCO_2). This acidemia might be induced by the acid solution or by the protein infused. IVIG preparations should be used with caution in patients with conditions which may impair their ability to compensate for a large acid load.

The relatively small decrease in the number of red cells after IVIG infusion, which was constant for different flow rates, may be due to the dilution factor. The higher percentage decrease in white cells, however, cannot be attributed to hemodilution. Considering that the infused volume was smaller when more concentrated IVIG preparations were used, the sharp decrease in white-cell numbers seems to be caused by the infused IgG. Transient neutropenia following IVIG infusion has been described in a 36 year-old woman with systemic lupus erythmatosus[16] and in a newborn infant.[17] The cause of the neutropenia observed by these investigators and by us is unclear. It may be related to the presence of anti-leukocyte antibodies in IVIG or to the formation of immune complexes in the circulation which could attach to the Fc receptors present on circulating white cells.[9] O'Donnell et al. observed an increase in serum immune complex-like activity during and after IVIG infusions.[18] Another possibility is an altered expression of cell-surface CR3, the receptor for C3bi, after IVIG infusions with a consequent increase in adhesion of neutrophils to blood vessels.[18] An increase in leukocyte adhesion molecule expression may also occur, resulting in a higher adhesiveness to endothelial cells. We believe that increased transendothelial migration across the blood-brain barrier due to increased adhesion may present an explanation for the pleocytosis found in acute aseptic meningitis after IVIG infusion observed in some patients after IVIG infusion.

IVIG has been used successfully for treatment of idiopathic thrombocytopenic purpura. In these patients, a rise in platelet count has been observed within 24 hours with a peak increase about 10 days after therapy.[19,20] We observed a 20-30% decrease in platelets 5 minutes after infusion, possibly due to platelet aggregation induced by circulating immune complexes. None of our patients manifested bleeding after IVIG infusion. Since the doses of IgG utilized in the treatment of autoimmune diseases are higher, our results suggest that the immediate effect of IVIG on platelets need to be monitored in patients with low platelet counts or other coagulation problems.

From the observations made thus far, we conclude that high infusion rates with high-concentration IVIG preparations induce significant immediate metabolic and hematologic changes. In future studies, it will be important to follow patients until the changes in laboratory parameters reported here return to normal after IVIG infusion. While high infusion rates may be tolerated clinically by the majority of patients, changes observed may be implicated in the adverse effects observed in some patients. We recommend calculating infusion rates based on mg/kg/min and monitoring patients carefully during and after IVIG infusions. The advantages of using high infusion rates have to be re-evaluated keeping in mind the potential side effects, especially in high-risk patients such as with cardiac and renal diseases and hypergammaglobulinemia (AIDS). We also encourage reporting the side effects of the use of high IgG infusion rates, since our experience suggests that incidents attributable to the use of IVIG may be more frequent than presently assumed.

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RESUMO

Objetivo: Nós pretendemos investigar se o aumento de velocidade de infusão de gamaglobulina intravenosa (IVIG), está associada com alterações metabólicas e hematológicas em pacientes com deficiência de anticorpo. **Casuística e Método:** Nós estudamos sete pacientes (2-16 anos) com deficiência primária de anticorpo que já estavam em tratamento com reposição regular de IgG, na dose de 350-600 mg/kg a cada três semanas em preparados a 3%, por períodos de seis meses a quatro anos. Inicialmente a concentração dos preparados de IVIG foi aumentando para 6, 9 e 12% em infusões consecutivas numa velocidade constante 4 mg/kg/min. Subseqüentemente, na segunda fase do estudo, mantivemos a concentração a 12% e a velocidade de infusão foi aumentando para 8, 12, e 16 mg/kg/min. **Resultados:** Clinicamente, todos os pacientes toleraram o aumento da concentração de IVIG na velocidade constante de 4 mg/kg/min. Entretanto, 3 pacientes apresentaram efeitos colaterais quando a velocidade de infusão aumentou para 8 e 16 mg/kg/min. **Conclusão:** Nós concluímos que alterações metabólicas e hematológicas podem ocorrer quando se administra preparados de IVIG em altas concentração e velocidade mesmo que os pacientes tolerem bem clinicamente. As vantagens de utilizar velocidades elevadas na infusão de IVIG devem ser reavaliadas.