

Rapid infusion of Sandoglobulin in patients with primary humoral immunodeficiency

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We studied 16 patients with primary disorders of humoral immunity to determine the practicality of infusing intravenous gamma globulin at rates of infusion and concentrations higher than the 4 mg/kg/min and 6% currently recommended. In the first portion of the study, the concentration of Sandoglobulin was increased from 6% to 12%. In the second portion, the flow rate was increased to 5 mg/kg/min, and if no reactions occurred, the time of each successive infusion was decreased by 10 minutes until infusions were completed in 15 to 20 minutes or vasomotor reactions occurred. Thirteen of the 16 patients completed the study; six patients achieved reaction-free rates >15 mg/kg/min, and the other patients achieved rates ranging from 7.1 to 12 mg/kg/min. Seven patients had infusion times <30 minutes, with four patients completing infusions in 15 minutes. In the 13 patients who completed the study, there were 14 reactions in 159 infusions, mostly fever and chills, and often at the end or after the infusion. Only one infusion could not be completed because of an adverse reaction. Three patients were not able to complete the study because of adverse reactions; there were seven reactions in 11 infusions in these three patients, although none of the reactions were considered serious. Overall, in this study, most immunodeficient patients (13/16) were able to tolerate infusion rates of Sandoglobulin two to 10 times higher than the standard rates now recommended. The maximal rate of infusion must be individualized, but for carefully selected patients, infusions of 400 mg/kg can be completed in 1 hour or less. Such short infusion times could greatly decrease the amount of time lost from work or school and thus improve compliance. (J ALLERGY CLIN IMMUNOL 1991;88:61-7.)

Key words: Intravenous gamma globulin, immune serum globulin, primary humoral immunodeficiency

Human ISG has been used to treat patients with humoral immune deficiency since 1952. The Cohn fraction II ISG that was then available caused severe systemic reactions when it was infused intravenously¹; therefore, it had to be administered intramuscularly. Not only were injections of ISG preparations painful, but the amount of gamma globulin that could be injected was quite limited. The 100 mg/kg/mo dose of

Abbreviations used

IVIG: Intravenous immunoglobulin
ISG: Immune serum globulin

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ISG, recommended by Janeway and Rosen,² was determined, in part, on these practical limitations. The availability for the past decade of intravenous immunoglobulin (IVIG) preparations^{3,4} has removed the limitation on the amount of IgG that can be administered. Low doses appeared to prevent serious infections in immunodeficient patients, and although it was not possible to prove that higher doses were more efficacious,⁵ some studies suggested that patients had fewer infections after receiving higher doses.^{6,7} In addition, we observed in our patients that specific antibody titers were extremely low 4 weeks after an infusion of 100 mg/kg of IVIG. Based on these observations, IVIG doses of 400 mg/kg administered

every 3 to 4 weeks are now becoming standard for the treatment of immunodeficiency, and even higher doses are recommended for the treatment of immune thrombocytopenic purpura and Kawasaki disease.^{8,9}

The first IVIG preparations caused a high incidence of phlogistic and anaphylactoid side effects that were rate dependent,^{3,10} but the second and third generation IVIG preparations have been well tolerated by most patients. The rates of the infusions approved by the Bureau of Biologics and recommended in the product literature are based on rates used in the original studies evaluating the safety and efficacy of IVIG,^{1,3,4} and no studies have attempted to determine the maximum tolerated rate.

According to product literature, the recommended rate of infusion for Gammagard (Hyland Therapeutics, Glendale, Calif.) is 0.4 to 3.3 mg/kg/min; the infusions are begun at the lower rate and increased stepwise as tolerated. The recommended rates for Gamimune N (Cutter Biological, West Haven, Conn.) are 0.5 to 4 mg/kg/min. The rates advised for Sandoglobulin (Sandoz Pharmaceutical Corp., East Hanover, N.J.) are 15 to 60 mg/min without regard to the weight of the patient. The maximum rate equates to 3 mg/kg/min for a 50 kg patient. At these rates, the infusion of 400 mg/kg usually requires at least 2 hours, or longer if the rates are not increased promptly at 15-minute intervals. Infusions of IVIG are now administered routinely in an outpatient setting in a doctor's office or an infusion center. Infusions necessitate time off from school or work; thus, shorter infusion times would minimize absenteeism and make treatment more acceptable and less costly.

Our experience during the past 15 years has been that most immunodeficient patients, especially children, tolerate the currently available IVIG preparations at standard rates of infusion without any adverse effects. Several patients have inadvertently received infusions at several times the standard rate without reaction, suggesting that much higher rates would be tolerated. The studies reported here demonstrate that this is indeed the case.

MATERIAL AND METHODS

Patient selection

Sixteen patients with primary disorders of humoral immunity were enrolled in the study. One patient with Nezelof syndrome, one patient with common variable immunodeficiency, and two patients with Wiskott-Aldrich syndrome had mild T cell abnormalities. The patients ranged from 6 to 29 years of age, and all had received IVIG without significant adverse reactions for several years, although four of the patients had experienced occasional mild reactions with various IVIG preparations. Several patients had par-

ticipated in previous trials of other IVIG preparations. Patients with a significant history of intolerance to IVIG preparations, patients with diabetes or renal disease, and pregnant women were excluded. Informed consent was obtained at each visit from the patient or guardian, and the study was conducted with the approval of the Institutional Review Board of Duke University.

Study medication

Sandoglobulin is produced by the Swiss Red Cross and marketed by Sandoz. It has been used for >8 years, and there have been in excess of 4 million infusions worldwide. It is provided as a lyophilized powder containing sucrose, but no sodium chloride, which is in the diluent. Thus, Sandoglobulin can be reconstituted at any concentration without causing an excessive saline concentration. A 12% solution was the maximum that was practical without excessive viscosity. The osmolarity of the 12% solution was 1074 mOsm/L, compared to 498 mOsm/L for a 3%, 690 mOsm/L for a 6%, and 882 mOsm/L for a 9% solution.

Study design

Infusions were administered in the outpatient unit of the Clinical Research Unit (RR30). No patient was pretreated with aspirin or antihistamines. All patients continued the IVIG dose and schedule that they had been receiving before this study. No patient received <400 mg/kg/mo, and in general, the doses were chosen to provide trough IgG concentrations at least 300 mg/dl above baseline. The effect of increasing the concentration of Sandoglobulin was determined in the first three infusions. The concentration of Sandoglobulin was increased from 6% to 9% and then to 12%, whereas the flow rate was decreased to maintain a maximum rate of 2 mg/kg/min. After the 12% solution was tolerated, the next infusion was administered at 2 mg/kg/min for 15 minutes and increased every 15 minutes to a maximum of 5 mg/kg/min. For subsequent visits, the infusion was begun at the maximum rate that had been tolerated previously, and the time required for each successive infusion was decreased by 10 minutes per infusion until the infusion was completed in 15 to 20 minutes or adverse reactions occurred. An infusion pump was used to ensure accurate flow rates. Complete blood counts, liver transaminases, and immunoglobulin concentrations were determined before the first three infusions, before every third infusion, and at the conclusion of the study. Vital signs were monitored before, during, and for 15 minutes after each infusion. Adverse reactions were recorded in detail.

RESULTS

The infusion rates and reactions are summarized in Table I. Thirteen of the 16 patients were able to complete the study. The minimum time of infusion was 15 minutes, and seven patients were able to complete the infusion in 30 minutes or less. Of the patients completing the study, all completed their infusions within 75 minutes, and in several cases, the infusion time was limited by the intravenous flow rate rather

TABLE I. Infusion record during rapid infusion of Sandoglobulin

Pt No.	Min time (minutes)	Max rate (mg/kg/min)		No. of infusions				Study completed
		All	No Rxn	Total	With Rxn	Interrupted	Incomplete	
1	15	30.6	30.6	14	0	0	0	Yes
2	46	8.1	8.1	8	0	0	0	Yes
3	50	7.7	7.7	8	0	0	0	Yes
4	50	8.0	8.0	12	0	0	0	Yes
5	20	24.2	24.2	14	0	0	0	Yes
6	25	16.2	16.2	13	3	0	1	Yes
7	80	8.2	—	2	2	1	1	No
8	40	10.4	10.4	11	0	0	0	Yes
9	105	6.0	5.0	3	2	1	1	No
10	15	26.9	26.9	14	0	0	0	Yes
11	60	10.6	9.9	13	3	1	0	Yes
12	15	25.8	25.8	14	0	0	0	Yes
13	35	14.9	4.9	6	3	1	1	No
14	15	26.8	24.2	14	1	0	0	Yes
15	30	13.1	7.1	14	5	1	0	Yes
16	75	12.0	12.0	10	2	1	0	Yes
Total				170	21	6	4	13/16

Pt, Patient; Min, minimum; Max, maximum; Rxn, reaction.

than by the onset of adverse reactions. Maximum rates of infusion ranged as high as 30.6 mg/kg/min, with eight patients achieving >10 mg/kg/min without adverse reactions. Two other patients, Nos. 13 and 15, achieved higher rates but had adverse reactions that required slowing the rate.

There were 21 reactions in a total of 170 infusions; seven of the reactions occurred in the three patients who were unable to complete the study. Only four infusions could not be completed because of adverse reactions, with three of these occurring in the group that dropped from the study. Six infusions were slowed or interrupted briefly but were later completed without incident.

Details of the adverse reactions are presented in Table II. The reactions occurring in the three patients that were unable to complete the study are presented in the upper section of the Table. In general, the patients who would have difficulty with the infusions were identified early in the study.

Patient 7 had severe lung disease at the time of the study. He became agitated and irritable during the first infusion but received the full dose at a slower rate. During the second infusion, he again became agitated, irritable, and complained of pain at the intravenous site. The infusion was slowed, but he continued to complain of pain and the infusion was stopped. The family elected to withdraw him from the study.

Patient 9 had fever and chills 2 hours after the first infusion was completed. He received another infusion of 6% Sandoglobulin at the next visit and had no difficulty. The third infusion was administered with 9% Sandoglobulin, and he had no problem during the infusion. However, as the infusion was completed, he complained of fever and shaking chills and was noted to have dusky lips. He had no respiratory distress, and oxygen saturation was normal. He was administered an aspirin and was infused with normal saline. His symptoms resolved within 90 minutes without specific medications.

The third patient, no. 13, complained of some knee pain at the end of the first infusion but tolerated the next three infusions without difficulty. She developed fever, chills, nausea, and diarrhea at the end of the fifth infusion of 12% Sandoglobulin, which had been administered at 14.9 mg/kg/min. She improved within 90 minutes after receiving aspirin and an infusion of normal saline. She had a similar reaction during the sixth infusion. The infusion was stopped after 41 ml of a planned 50 ml had been administered, and the family elected to withdraw her from the study.

The 14 reactions that occurred in the 13 patients completing the study are summarized in the lower section of Table II. Eight patients had no reactions during the study. Only two reactions were significant enough to require stopping the infusion, and one of

TABLE II. Details of adverse reactions during rapid infusion of Sandoglobulin

Pt No.	Infusion No.	Conc (%)	Rate (mg/kg/min)	Amount infused (ml)	Rxn	Intervention
Not completing the study						
7	1	6	6.16	10	Agitated Irritable	Infusion slowed Completed
	2	9	4.10	25	Agitated Irritable Back pain Local pain	Infusion slowed then stopped Only 30/66 ml in- fused
9	1	6	5.98	350	Fever Chills 2 hr after infusion	Aspirin Resolved in 2 hr
	3	9	3.67	222	Dusky lips Shaking Chills at com- pletion	Aspirin, normal saline Resolved in 90 min
13	1	6	5.00	85	Knee pain at end	Aspirin
	5	12	14.90	50	Fever Chills Nausea Diarrhea at end	Aspirin, normal saline Resolved in 90 min
	6	12	9.09	41	Fever Chills during infusion, 41/50 ml	Aspirin, normal saline Resolved in 30 min
Completing the study						
6	3	12	3.23	45	Cold Irritable Crying Vomiting, 45/75 ml	Infusion stopped Normal saline
	7	12	29.10	100	Chills Nausea 35 min after com- pletion	Normal saline Resolved in 15 min

Pt, Patient; Rxn, reaction; BP, blood pressure.

*McNeil Consumer Products, Fort Washington, Pa.

†Parke-Davis Consumer Products, Morris Plains, N.J.

those infusions, No. 9 for patient 11, was completed with a lower concentration of Sandoglobulin. Patient 6 complained of feeling cold and had a marked mood change with crying and irritability 45 minutes into the third infusion with 12% Sandoglobulin. The infusion was interrupted after she received only 45 ml of a planned 75 ml of Sandoglobulin and normal saline was administered. She had milder reactions during the seventh and ninth infusions but was able to complete 13 infusions. She ultimately attained a rate of 16.2 mg/kg/min and completed an infusion in 25 minutes. Patient 11 had fever and chills after the completion of infusions 4 and 7, then complained of difficulty

breathing during infusion 9. No wheezing or respiratory distress was noted. The infusion was stopped for 20 minutes and then resumed with a 6% solution. He tolerated subsequent infusions with the 12% solution, and he attained a maximum reaction-free rate of 9.9 mg/kg/min and a 60-minute infusion time.

There were no significant abnormalities in blood counts, serum electrolytes, or hepatic transaminases during the course of the study.

DISCUSSION

Despite nearly 40 years of clinical experience with gamma globulin, the cause of adverse reactions is still

TABLE II. Cont'd

Pt No.	Infusion No.	Conc (%)	Rate (mg/kg/min)	Amount infused (ml)	Rxn	Intervention
11	9	12	6.63	30	Facial flushing	Slowed for 15 min
	4	12	4.99	250	Fever after completion	Aspirin
	7	12	8.70	275	Fever Chills 30 min after completion	Tylenol* Resolved in 30 min
	9	12	10.62	81	Difficulty breathing 15 min into infusion	Infusion stopped for 20 min Completed with 6% solution
14	14	12	26.84	300	Fever Chills 30 min after completion	Tylenol*
15	9	12	10.07	275	Itching eye-brows after completion	Resolved spontaneously
	10	12	13.07	275	Flushing Itching of face at end of infusion	Benadryl† Normal saline Resolved in 60 min
	11	12	12.98	275	Same as infusion No. 10	Normal saline
	12	12	6.59	206	Itching and flushing after 45 min	Rate slowed Completed at 4.31 mg/kg/min
	13	12	6.10	142	Itching and flushing after 45 min	Infusion slowed Completed at 5.9 mg/kg/min
16	6	12	6.72	70	BP increase from 120/80 to 150/100	Infusion slowed Completed at 4.5 mg/kg/min
	7	12	9.97	275	Chills after infusion	Normal saline

unknown. A small minority of patients with common variable immunodeficiency who are completely IgA deficient produce IgE anti-IgA antibodies that cause severe, life-threatening, anaphylactic reactions after only a few milliliters of IgA containing gamma globulin or plasma are infused.¹¹ Fortunately, such reactions are rare, and most patients have phlogistic reactions consisting of fever, chills, nausea, vomiting, back pain, and abdominal pain.^{1,3} Others have anaphylactoid reactions, including flushing, urticaria, chest tightness, and wheezing. Most of these reactions are rate dependent and respond to slowing or briefly interrupting the infusion.¹ Although the mechanism is not known, it has been hypothesized that either the IgG antibodies that are infused interact with antigens

or microorganisms in the infected host and initiate complement activation or that aggregates of IgG are able to do so independently of antigen.^{1,10} The reactions would then be due to the release of inflammatory mediators derived from complement and white cells. The IVIG products that are available today have all been demonstrated to be free of vasoactive amines and other potentially toxic contaminants.

The rates of infusion recommended by the manufacturers are based on rates used in the initial studies. These rates were quite conservative because the early IVIG preparations were not well tolerated. The rates are also limited, in part, by the concentration of IgG and the maximal flow rates that can be attained with peripheral veins. Sandoglobulin is furnished as a ly-

ophilized powder without sodium chloride, since saline is contained in the diluent. Thus, it can be reconstituted to any concentration and still maintain physiologic concentrations of sodium. The time required to dissolve Sandoglobulin to 9% and 12% concentrations was slightly longer than the time for the standard 6%, but the difference was not great enough to be considered a problem. Concentrations >12% proved to be too viscous for routine use, and even 12% was difficult to infuse rapidly through the small veins in some children. However, all concentrations of Sandoglobulin were well tolerated in this study, and only one patient complained of local pain that occurred with the 9% solution.

It is difficult to achieve such rapid rates of infusion merely by increasing the infusion rate of the standard 5% or 6% solutions of IVIG. The ability to infuse IVIG rapidly is not unique to Sandoglobulin, however. We have recently evaluated a 10% solution of an experimental preparation that could be infused at rates comparable to rates used in this study with a minimum of adverse reactions. It is not known if any of the other currently available IVIG preparations can be reconstituted to higher concentrations. Factors such as viscosity and osmolarity, as well as the presence of multimers of IgG, potentially could influence the tolerability of a given preparation. Dissolving the Sandoglobulin with water instead of saline appears to reduce the incidence of adverse reactions (Gelfand E. Personal communication), but this has not been evaluated in a controlled manner. Additional studies will be necessary to define these parameters and which preparations can be infused rapidly.

Eight of the patients had no reactions during the study. All the patients, including patients who could not complete the study, attained the routinely used rates of infusion of 3 to 4 mg/kg/min. Eight patients achieved rates >10 mg/kg/min. Several other patients could not reach the maximum rate because of difficult intravenous access. Only the three patients who dropped from the study and patients 11, 15, and 16 had reactions that limited the ultimate rate, although the latter achieved maximal reaction-free rates of 9.9, 7.1, and 12 mg/kg/min, respectively. All the adverse reactions in the 13 patients who completed the study occurred with the 12% solution of Sandoglobulin, and there was not a clear relationship between rate and incidence of adverse reactions. Many patients who experienced mild adverse events tolerated subsequent infusions at even higher rates.

It was not always possible to predict which patients could not tolerate rapid rates of infusion. Patients with known serious adverse reactions were not recruited; therefore, this was a selected population. However, patients 5 and 15 had a history of fever and chills with

Gammagard, No. 13 had a history of arthralgia with Gamimune N, and patient 15 also had had flushing and hives with Intraglobin (Biotest Pharma GmbH, Frankfurt, Germany). Of these patients, No. 5 had no reactions, No. 13 dropped from the study, and No. 15 had five episodes of flushing and urticaria. Thus, stricter entry criteria would have eliminated two of the patients who had reactions. Patient 9 had severe lung disease, and the presence of chronic infection may have contributed to the onset of his reactions.

Of the patients with adverse reactions, only patient 9 had a reaction that was severe enough that additional infusions were considered unwise. The other patients were removed at their parents' request because the reactions made them uncomfortable and were an additional burden in an already sick child. However, the reactions were not considered to be severe or life-threatening and no medications were required. The three patients had problems early in the study, and in clinical practice, such patients would be readily identified and could continue at lower rates of infusion. Importantly, despite the incidence of mild reactions, all the patients who completed the study preferred the high rates of infusion.

For most patients, 13 of 16 in this study, rapid infusions were safe and well tolerated. Each patient had a different tolerance for high rates of infusion, and some patients may tolerate a specific IGIV preparation better than other patients. If infusions are administered under carefully controlled circumstances, the rates of infusion can be increased stepwise until a maximally tolerated rate for that patient is attained. With 12% Sandoglobulin, rates of four to five times rates currently recommended can be attained in most patients, and some patients can achieve rates 10 times rates currently used. Total infusion times of 20 minutes should be possible for patients receiving 400 mg/kg. The amount of time lost from work or school could be reduced, which would improve patient acceptability. However, since the risk of adverse reactions is increased during rapid infusions, they cannot be recommended for patients who receive their infusions outside of medical facilities. In addition, the medical condition of the patient must be considered before attempting rapid infusions. For example, patients with Kawasaki disease may have cardiomyopathy that would preclude rapid infusions of any solution, including IVIG. Additional studies are needed before the observations in this study can be extrapolated to other patients.

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