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RELATIONSHIP OF THE DOSE OF INTRAVENOUS GAMMAGLOBULIN TO THE PREVENTION OF INFECTIONS IN ADULTS WITH COMMON VARIABLE IMMUNODEFICIENCY

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Abstract—The objective was to assess clinical efficacy of 3 dosages of intravenous gammaglobulins to prevent infectious episodes in adult common variable immunodeficiency. We designed a randomized, double blind, dose-assessing study. The setting was at University Hospital, Out-Patient Clinic. Our patients were twenty-one adult patients with common variable immunodeficiency. The measurements were comparative study of the number and severity of infections using 3 various dosages of intravenous gammaglobulins, each given monthly for at least 6 months. Results indicated four hundred and eighty-four infectious episodes occurred while giving 305 infusions of IVIG 200 mg/kg; 205 infectious episodes while giving 170 infusions of 400 mg/kg and 436 infectious episodes while giving 247 infusions of 600 mg/kg. The morbidity scores (infection/infusion) were 1.59, 1.21 and 1.77 respectively (p – N/S). There was no significant difference in the severity of infections on the above 3 dosages, and no difference in the duration of infection-free intervals. The conclusions resulted in no significant differences in morbidity in adult patients with common variable immunodeficiency treated in cross-over pattern with IVIG 200 mg/kg, 400 mg/kg and 600 mg/kg. Thus, high dosages of IVIG are not conferring better protection against infections in such patients.

INTRODUCTION

Administration of gammaglobulin has been established as a useful treatment for common variable immunodeficiencies (1–4). The effectiveness of intravenous

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administration of gammaglobulin (IVIG) as compared to untreated patients or those who received intramuscular preparations has also been well established (1, 2, 4–7). Reduction in the incidence and severity of sino-pulmonary infections has been well documented (2–4). Furthermore, use of IVIG may confer social and economic benefits through a lower rate of absenteeism and hospitalizations.

The beneficial effect of IVIG has been initially attributed to the increase and maintenance of the level of circulating IgG (4, 7–9). Indeed IVIG infusions maintain all four subclasses of IgG in the circulation for about 16–30 days (9), especially when the dosages of 400 mg/kg/month or more are administered (10). More recent studies have shown however that IVIG may exert beneficial effect on immunological system in a much more complex way than merely increasing the concentration of circulating immunoglobulins. IVIG was found to downregulate Fc receptors on the reticuloendothelial cells, to delete immature lymphocytes, activate mature CD4 T and B cells and downregulate some cytokine secretion and activity (11–16).

However, the dosage of IVIG administered to patients with humoral immunodeficiencies should be related primarily to the attenuating and/or preventive effect on infectious episodes and not merely to its pharmacodynamic and immunological characteristics. Since adult patients with common variable immunodeficiency generally have well functioning cellular immunity system, they usually have normal antiviral defenses (7) and therefore the assessment of the efficacy of IVIG should reflect primarily their impact on bacterial infections.

IVIG has been in clinical use for over 30 years (17) yet there is little information about the clinically optimal dosage and frequency of infusions of IVIG. Statement from the NIH Consensus Development Conference conducted in 1990 and in the following editorial (1), emphasized the paucity of controlled trials evaluating different dosage regimens of IVIG. It was shown that monthly administration of as little as 200 to as much as 800 mg/kg is usually adequate to maintain plasma immunoglobulin levels at about 500 mg/dl (4, 7, 10, 18, 19). However, such a wide range of dosages may not be equally beneficial in reducing the number and severity of infectious episodes.

The present study compared three different dosages of IVIG administered in regular monthly intervals to adult patients with common variable immunodeficiency. The principal analysis examined both the quantity and quality of subsequent infections using suggested classification of infectious episodes (Table 1). The dosage in excess of 400 mg/kg did not provide better protection against infections, although it resulted in the highest immunoglobulin level in the blood. This finding may have both clinical and economical significance for IVIG administration.

MATERIALS AND METHODS

Twenty-one adult patients with common variable immunodeficiency and past history of frequent and severe sino-pulmonary infections were enrolled to the study. The diagnostic criteria for inclusion conformed to the established definition of common variable type of immunodeficiency with agammaglobulinemia (20). Patients were excluded if they had complement deficiency, concomitant malignant processes or other diseases that could potentially lead to infections. All patients were investigated, treated and followed up by the Immunodeficiency Clinic of the Division of Immunology of the University of Toronto.

The design was that of cross-over double blind cohort study. Patients received monthly infusions of IVIG (Iveegam, Immuno A.G. Vienna, Austria) and were randomly assigned to either 200, 400, or 600 mg/kg/mo regimen. After a period of at least 6 monthly infusions of one dosage, the patients were switched to another dosage. The new dosage continued for at least 6 months. If possible, the patient was then switched to a third dose for another 6 month interval. The patients were not aware of the administered dosage of IVIG. There was no clinical difference between the cohort which was started on a low dosage vs high dose of IVIG.

Before each infusion clinical details of the preceding month were recorded by the attending physician. Each patient received a diary and was instructed to record his/her health problems. For each patient an individual profile of infections was compiled describing the number and severity of infections occurring during a particular month. Furthermore at the end of the trial each patient was interviewed by an independent reviewer. The notes of family physicians were obtained as well. At the end of the trial composite clinical profiles were prepared including all the above mentioned sources of information.

Infections were divided into 3 categories—mild, moderate and severe (Table 1). The above infections were then grouped according to the dosage of IVIG that had been given at the beginning of the particular month. Thus, the patient-month rather than the patient was the unit-of-analysis for statistical testing. Statistical analysis consisted mainly of X^2 tests to assess the relationship between

Table 1. Examples of Infections Classified into Mild, Moderate and Severe[a]

Mild	Moderate	Severe
Nasal discharge	Sinusitis[b]	Pneumonia
"Head" or "chest" cold	Bronchitis	Pleurisy
Flu-like illness	Pharyngitis	Acute sinusitis[b]
Conjunctivitis	Laryngitis	Acute abscesses
Diarrhea	Otitis	Sepsis
Vaginal infection	Fever[c]	Acute Osteomyelitis
Oral Candida	Urinary tract infection	
Afebrile enteritis		

[a]Moderate infections did not require bed rest or absence from work. Severe infections always required bed rest or hospitalization and absence from work.
[b]Moderate sinusitis-pressure, headaches
Severe sinusitis-with fever, positive x-rays and necessity of antibiotics
[c]Fever of unknown origin lasting no more than 3 days

dosage and the number of infections, and the severity of infections. ANOVA regression program was also used to determine the difference in morbidity score between the dosages.

Since the aim of this study was to compare the efficacy of 3 different dosages of IVIG, there was no placebo-controlled group included.

RESULTS

Twenty-one patients received a total of 722 monthly infusions of IVIG. The average duration of follow-up was 34 months (range 18–65-months). The initial dose of IVIG was either 200 mg/kg, 400 mg/kg or 600 mg/kg, chosen randomly without knowledge of the patient. Each dosage was given for at least 6 months.

During the total duration of follow up of 722 months, the patients had 1125 infections. (Table 2). The infections were divided into mild (n = 273), moderate (n = 758) and severe (n = 94) (Table 1). The percentage of patients who contracted infections during a given month varied from 54% to 68%. The average number of infections per month varied from 1.21 to 1.77. (Table 2). The severity of infections varied, the moderate group being the commonest (Table 2). Number of post-infusion months when infections occurred, varied from 54% to 68%. (Table 3). In the months when infections occurred, the number of episodes of infections varied, but was similar in the three dosage groups (Table 3). The highest number of infection-free months occurred when the patients received IVIG at the dose of 400 mg/kg/mo, however the difference comparing 200 and 600 mg/kg dosages was not statistically significant.

Twenty-six episodes of minor adverse reactions occurred during 722 infusions (3.6%). These included 10 episodes of polyarthralgia, 7 episodes of tran-

Table 2. Relationship of I.V. Gammaglobulin Dosage to Infections

IVIG (mg/kg)	Number of Infusions	Number of Infections	Morbidity Score Infection/ Infusion[b]	Severity of Infections (%)[a]		
				Mild (%)	Moderate (%)	Severe (%)
200	305	484	1.59	118 (24.4)	333 (68.8)	33 (6.8)
400	170	205	1.21	53 (25.9)	132 (64.4)	20 (9.8)
600	247	436	1.77	102 (23.4)	293 (67.2)	41 (9.4)
Total	722	1125	1.52	273 (24)	758 (67)	94 (8)

[a] Difference in morbidity scores: not significant.
[b] Dependence of severity of infections to dosage: not significant.

Table 3. Number of Episodes of Infection in Post-Infusion Months in Which the Patients Had Infection[a]

IVIG (mg/kg)	Number of months	Months without episodes of infection	Months with episodes of infection	Infection/ month score	Number of Episodes per month			
					1	2	3	≥4
200	305	106 (35%)	199 (65%)	2.43	73 (37%)	45 (23%)	35 (18%)	46 (23%)
400	170	78 (46%)	92 (54%)	2.23	31 (34%)	33 (36%)	14 (15%)	14 (15%)
600	247	78 (32%)	169 (68%)	2.58	49 (29%)	52 (31%)	28 (17%)	40 (24%)

[a]Dependence of number of episodes to dosage: not significant.

sient fever and 2 episodes of pruritic skin rash. Other seven episodes consisted of transient shortness of breath or watery eyes and flushing. There were no anaphylactic reactions, angioedema or hypotension, and all reactions resolved in less than 24 hours. Nine reactions occurred when the patients received IVIG 200 mg/kg, 4 on the dose of 400 mg/kg and 13 on the dose of 600 mg/kg. In relation to the number of infusions in each dose-category, adverse reactions occurred in 4.5% of infusions of 200 mg/kg, 2.4% of infusions of 400 mg/kg and 5.3% of infusions of 600 mg/kg.

DISCUSSION

Since the introduction of intravenous gammaglobulins (IVIG) into clinical practice (17) the effectiveness of IVIG preparations in therapy of primary immunodeficiencies has been well established (2). However the optimal dosages and treatment schedules have not yet been standardized. There is still a paucity of controlled trials to show clinical efficacy of IVIG in relation to the dosage regimens (2, 5, 10, 18).

There are conflicting reports comparing the effectiveness of different dosages of IVIG. One study reported that the increase of IVIG from 100 to 200 or even to 400 mg/kg/4w did not reduce the occurrence of infections (10). Another report concluded that the optimal dose of IVIG is 150–200 mg/kg/4w (7). Yet another report suggested that a monthly dose of 500 mg/kg reduced the number of infections more efficiently than 150 mg/kg (21). These studies were not blinded or randomized. To our knowledge, the only well controlled, cross-over study was done in a group of 12 children with primary immunodeficiency who received IVIG 150 mg/kg/mo for 1 year and 500 mg/kg/mo for another year.

The authors observed marked reduction in the incidence of sinusitis, pneumonia, diarrhea and arthritis when the higher dose of IVIG was administered (5).

Our study seems to be the first blinded cross-over study, using three different concentrations of IVIG in adult patients with common variable immunodeficiency. The intervals between the infusions were kept constant (4 weeks), in order to assess the relationship between dosage, number and severity of infectious episodes. Our results suggested that the dose of 400 mg/kg/mo tended to be more effective than that of 200 mg/kg/mo, although the differences were not statistically significant. The dosage increase to 600 mg/kg/mo did not result in better protection.

Our study confirms other reports indicating that administration of IVIG seldom causes adverse reactions and that they are usually minor (2, 5, 7, 18, 19). In our patients the overall incidence of adverse reactions was 3.6% and all were minor and transient.

It can be concluded that in adult patients with common variable immunodeficiency the dose of IVIG higher than 400 mg/kg/mo may not be necessary since it does not confer better protection against infections.

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