Bioavailability of γ-Globulin After Subcutaneous Infusions in Patients with Common Variable Immunodeficiency

J. WANIEWSKI, 1 A. GARDULF, 2 and L. HAMMARSTRÖM 2,3

Accepted: October 1, 1993

Replacement therapy, using subcutaneous infusions of γ-globulin, is being applied increasingly for antibody-deficient patients, as this form of treatment has been found to be related to a very low frequency of adverse systemic reactions. However, the uptake of IgG from subcutaneous tissue may be low, owing to degradation locally, especially for the IgG3 molecule. Therefore, the kinetics of IgG and IgG subclass concentrations in the sera of 23 patients with common variable immunodeficiency was investigated during 18 months of subcutaneous infusions of γ-globulin (100 mg/kg/week). Seventeen patients were previously treated with intramuscular injections or intravenous infusions. The mean serum IgG level increased twice in the previously treated patients and four times in the previously untreated patients. A steady state was reached after 6 months if the subcutaneous infusions were given weekly and after 1 week if the patients were given daily infusions for 5 consecutive days and, thereafter, weekly infusions. The fractional catabolic rate of IgG (4.1-5.9% per day) was found to be at the lower limit reported for normal control subjects, if 100% bioavailability of the infused IgG was assumed. The fractional contents of IgG subclasses in the patients' serum IgG resembled the physiological pattern, with the exception of IgG4, which was not present in the γ-globulin preparations used. Significantly increased levels of IgG1 and -2 were seen in both previously treated and untreated patients during the treatment.

KEY WORDS: Common variable immunodeficiency; subcutaneous infusions; γ-globulin; bioavailability; fractional catabolic rate.

INTRODUCTION

Replacement therapy with γ-globulin in antibody-deficient patients can be given as intramuscular injections and intravenous or subcutaneous infusions (1–8). The kinetic properties of γ-globulin given intravenously to patients with primary immunodeficiency diseases have been evaluated previously in a few studies. The half-lives for IgG and IgG subclasses reported in those studies were much longer than for normal control subjects (1–4). However, the mathematical methods applied for the calculations of half-lives were based on the false assumption of steady state and have therefore recently been criticized and the results considered biologically and therapeutically absurd (5).

The kinetics of IgG antibodies after a single intramuscular or subcutaneous injection has been investigated previously in healthy volunteers, using anti-Rh immunoglobulin (7). It was shown that the kinetic characteristics of the investigated antibodies depended on the form and site of the injection. The half-lives and catabolic rates were close to the average values in normal controls or higher. The uptake rates tended to be higher for the intramuscularly than for the subcutaneously injected anti-Rh immunoglobulin (7).

As subcutaneous infusions of γ-globulin have been found to be related to a very low frequency of adverse systemic reactions and are appreciated by patients (8), subcutaneous therapy is being used more frequently. However, the uptake of IgG after subcutaneous infusions may be low, owing to its short half-life and sensitivity to proteolytic degradation. It is therefore important to estimate the uptake of IgG and IgG subclasses from the subcutaneous tissue.

The objectives of the current study were to investigate the kinetic properties of IgG and the
four IgG subclasses during treatment by subcutaneous infusion of patients with primary hypogammaglobulinaemia. Furthermore, the kinetics of IgG was compared in two groups of patients: individuals previously treated with intramuscular injections of γ-globulin and patients not previously treated with immunoglobulins. Two schedules of subcutaneous therapy were also assessed: (i) weekly infusions of a constant dose of γ-globulin and (ii) daily infusions of γ-globulin for the first 5 days of treatment and weekly thereafter.

PATIENTS AND METHODS

Patients. Twenty-three patients—14 females and 9 males—with common variable immunodeficiency (CVID) and increased infection rate were included in the study. The diagnosis of CVID was set according to the WHO criteria (9) but with a local modification, i.e., a serum IgG level of <3, or <5 g/L combined with an increased rate of infections, and low levels of IgA and/or IgM. The patients were between 18 and 72 years of age (mean, 43 years).

Subcutaneous Treatment. At the time of the study, the patients had been on subcutaneous γ-globulin treatment for at least 18 months. All patients received a mercury-free, human immunoglobulin preparation (165 mg/ml) for intramuscular use (Gammaglobulin Kab, KabiPharmacia, Sweden). The infusions were given at a dose of 100 mg/kg/week with the exception of two patients, who received 157 and 183 mg/kg/week, respectively, owing to a very high rate of infections. The infusions were given in the abdominal wall, the thigh, or both, and the total γ-globulin amount was divided between two and six infusion sites (8).

Seventeen of the patients had, before subcutaneous therapy, been treated with intramuscular injections or intravenous infusions of γ-globulin. Eleven of these seventeen patients (Group I) received the subcutaneous therapy as weekly infusions (100 mg/kg/week), whereas in the remaining six patients (Group II) the treatment was carried out as daily infusions (100 mg/kg/day) for 5 consecutive days during the first week of treatment and as weekly infusions thereafter (100 mg/kg/week). Six patients (Group III) had, before subcutaneous therapy, never been treated with any form of γ-globulin. In Group III, subcutaneous treatment was carried out only as weekly subcutaneous infusions from the beginning (100 mg/kg/week).

IgG and IgG-Subclass Measurements. The IgG levels at the time of diagnosis for patients in Groups I and Group II were taken from their medical reports. Blood samples were collected in all patients before and after 6, 12, and 18 months of subcutaneous treatment. Blood samples were also collected after 1 and 2 weeks and after 1, 2, 3, 4, and 5 months of treatment in patients in Group II and Group III. The blood samples were always collected in connection with the actual infusion, i.e., as preinfusion samples. Blood samples were also collected every 24 hr between two consecutive infusions in one patient from Group I after 7 months of subcutaneous treatment.

Serum IgG concentrations were measured in all collected samples. Concentrations of IgG1, -2, -3, and -4 subclasses were measured in samples from patients in Groups II and III before and after 6 and 12 months of the subcutaneous treatment. Concentrations of IgG subclasses were assessed, using a radial immunodiffusion technique with monoclonal, antisubclass antibodies. Agarose (1%) was cast with polyethylene glycol (PEG; 7%) and predetermined amounts of the respective monoclonals. The antibodies used were as follows; IgG1, NL 16 (BAM 15); IgG2, GOM 1 (BAM 10); IgG3, ZG 4 (BAM 8); and IgG4, RJ 4 (BAM 11) and GB 7B (BAM 16) (Seward Laboratories, Bedford, UK). Serum samples (4 ml) were applied neat or diluted 1:10. A standard curve was determined for each plate by including serial dilutions of a reference serum SPS-01. The concentration of IgG in serum and in randomly sampled γ-globulin preparations was measured using rate nephelometry (Beckman Instruments AB, Sweden).

Calculations. The average rate of IgG delivery was calculated as the amount of infused IgG (dose volume * concentration) divided by the time between two consecutive infusions. The effective uptake of the infused immunoglobulin, G, was defined as the average rate of infusion which would have been necessary for the maintenance of the observed, steady-state value of the serum immunoglobulin concentration. The bioavailability of the infused immunoglobulin was calculated as the ratio of effective uptake to the average rate of IgG delivery.

The kinetic parameters of IgG (generation rate, effective uptake of infused IgG, fractional catabolic rate, etc.) cannot be estimated by using only routinely collected clinical data; a special turnover study with radioactively labeled IgG must be per-