Journal of Clinical Immunology, Vol. 13, No. 2, 1993

Half-Life of the Maternal IgG1 Allotype in Infants

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Accepted: December 1, 1992

The residence time of maternal IgG1 in the circulation of infants was measured by monitoring f-allotypic IgG1 or f-positive tetanus toxoid antibody in genetically $G1m^f$-negative infants. $G1m^a$-positive maternal tetanus toxoid antibody was similarly monitored in genetically a-negative infants. Blood samples were taken from infants at the age of 1–3 days, ca. 4 months, and ca. 6 months. An exponential decay at the same rate took place from age 1–3 days to 4 months and for the 2 subsequent months. The average concentration of the maternal IgG1 had dropped to ca. 10% of the 1- to 3-day value in 4 months and to ca. 3% in 6 months. The drop was due mainly to clearance but partly also to the weight increase of the child (doubling in 6 months). By correcting for the weight increase, we calculated that ca. 17 and 7% of the original maternal IgG1 was still present at ages 4 and 6 months, respectively. The average half-life of the maternal IgG1 was thus 48.4 days. The concentration of endogenous IgG1 in the cord blood was determined by studying a separate series of mother–newborn pairs. Assuming that cross-reactions of antiallotype reagents had no effect, the highest measured concentration of f-positive IgG1 in infants of f-negative mothers was 10 mg/L, half a percent of adult heterozygote values. Crossreaction may have played a role, however, and the value must be considered the upper limit of the true concentration.

KEY WORDS: Half-life; IgG; Gm allotypes.

INTRODUCTION

Several investigators have found an exponential decay of passively administered allogeneic immunoglobulins in the circulation of animals and humans (1–5). The decay might result from an enzymatic breakage of one or a few peptide bond(s) which initiates the breakdown of a molecule. From the decay curves, half-lives in the serum for the various IgG isotypes have been calculated.

While the decay curves have been strictly exponential in some circumstances, it has been reported that the half-life of human IgG depends on its concentration in blood (2). When the concentration was high, the half-life was short (11 days); when it was low, the half-life could be more than 50 days. These data can be explained by postulating that an exponential decay takes place but is modified by a "saving mechanism" with a limited capacity. For instance, it is possible that IgG molecules bound to Fc receptors enjoy a relative protection against enzymatic attack, but the Fc receptors of an adult can bind only a certain maximum amount of IgG (6).

Apart from the concentration-dependent variation in reported half-lives of human IgG, a large, apparently concentration independent variation is mentioned in published reports. The reported half-lives of human IgG [which must be dominated by the identical (1–3) half-lives of IgG1 and IgG2] vary from 12 to 96 days (Table I). The methods employed may account partly for the wide variations. In some published studies the survival of iodinated IgG in the circulation of recipients was measured. The iodination can alter IgG molecules and reduce their life span in the circulation. In fact, these studies have yielded short half-life values (Table I).

In other studies the life span of native IgG, either commercial intravenous IgG or maternal antibodies, has been determined. It was difficult to rule out a small endogenous production by the recipient of IgG or a specific antibody. If such production took place, it led to an erroneously long half-life.

A third type of error could have led to too short half-lives in some reports. When the decay of maternal antibodies in babies was measured, the dilution caused by the growth of the child was not always taken into the calculation.

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0271-9142/93/0300-0145$07.00/0

Table I. Reported Half-Lives in Circulation of Human IgG or IgG1 or IgG2[a]

Ref. No.	Nature of IgG	Reported half-life (days), mean, range
1	I-labeled myeloma proteins	12
2	I-labeled myeloma proteins	21
3	I-labeled myeloma proteins	21
4	I-labeled HGG	23
7	IGIV, unlabeled	33–43 (22–96)
8	IGIV, unlabeled	32–37 (17–85)
9	IGIV, unlabeled	30
10	IGIV, unlabeled	31
11	IGIV, unlabeled	26–30
12	IGIV, unlabeled (Premature infants)	33 (16)
7	Anti-TT	27–36
13	Hyperimmune antibody prep.	28
14	Hyperimmune antibody prep.	31 (20–66)
15	Maternal anti-DT	31.5[b]
16	Maternal anti-Rh	30[c]
17	Maternal antipolio	52.5 (50–55)
18	Maternal antipolio	37
19	Maternal antimeasles, -mumps, -rubella	35–40
20	Maternal antimeasles	46–53[c]
21	Maternal antimeasles	46–61

[a]IGIV, intravenous immunoglobulin; TT, tetanus toxoid; DT, diphtheria toxoid; HGG, human γ-globulin.
[b]The growth of the newborn was not taken into account in the calculation of the half-life.
[c]The growth of the newborn was taken into account in the calculation of the half-life.

The use of antiallotype reagents might eliminate several sources of error. When the mother has a Gm-allele (say f) that the baby lacks, the decay rates of f-type IgG1 in the baby can be monitored. Monitoring was difficult before the era of monoclonal antibodies, but now potent and sufficiently specific monoclonal anti-Gm antibodies are available. We have used anti-G1m(a) and anti-G1m(f) to determine the life span of maternal IgG1 in the baby's circulation.

MATERIALS AND METHODS

Serum Samples. Serum samples were obtained in connection of vaccine immunogenicity studies from healthy full-term infants at ages 1–4 days, ca. 4 months, ca. 6 months, and 14 months. Forty-seven of the children were the same as in Ref. 22; others were included in the IgG1 but not in anti-tetanus toxoid antibody determination.

Another series of serum samples from 75 newborns (umbilical cord) and their mothers was obtained from consecutive deliveries at the Department of Obstetrics and Gynecology, Helsinki University Central Hospital. The mothers were allotyped, and 13 $G1m^{a/a}$ homozygotes, the desired type, were found. The children of all these 13 mothers were normal; the birth weights varied between 3.0 and 4.2 kg, and the gestational age between 38 and 41 weeks. The study has been approved by the ethical committee of the Department of Obstetrics and Gynecology, Helsinki University Hospital.

Gm Allotyping. For allotyping the children we used serum samples taken at the age of ca. 14 months. Allotypic markers G1m(a) and G1m(f) were detected with a double-diffusion test (precipitation). Two monoclonal antibodies were used: anti-G1m(a) (5E7, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam) and anti-G1m(f) (clone GG-6, Bio Makor, Rehovot, Israel). The gels for the double-diffusion test contained 1% agarose (IsoGel Agarose, FMC BioProducts, Rockland, Maine), 2.7% (f-gels) or 3.8% (a-gels) polyethylene glycol 6000 (Fluka), 0.9% NaCl, and 0.02% sodium azide in 0.05 *M* phosphate, pH 7.4. Four microliters of serum and 2 μl of anti-a or anti-f ascites fluid were used. The plates were incubated at 4°C, and the precipitation was observed on the following day.

Quantitation of f-Positive IgG1. An inhibition test was used. Polystyrene plates (No. 655061, Greiner Labortechnik) were coated overnight with a serum (1/3000 diluted) from a $G1m^{f/f}$ homozygote. The plates were washed with 0.15 *M* NaCl–0.01% Tween 20–0.05% NaN_3 in 0.01 *M* phosphate, pH 7.4 (PBS-Tween). Serum samples were diluted with twofold steps in gelatin (5 g/L)-PBS-Tween. Each dilution was carefully prepared independently of the other dilutions. Aliquots (75 ml) of these dilutions were mixed with an equal amount of monoclonal anti-G1m(f) [clone 5F10 (23), Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam; 1/30,000]. The mixtures were incubated at room temperature for 4 hr, then aliquots of 100 ml were transferred to the coated plates. After an overnight incubation and washing, biotin-labeled rabbit anti-mouse immunoglobulin (Zymed 61-6040; 1/10,000 dilution in gelatin-PBS-Tween) was added and incubated overnight. Streptavidin–alkaline phosphatase (Dakopatts D 396) was applied at a 1/5000 dilution. After an overnight incubation the enzyme was quantitated with paranitrophenylphosphate. End-point titers were read by interpolation from the OD value that was in the middle between an uninhibited control and the maximally inhibited plateau.

Titers were converted to weight units by including in each session at least two sera of $G1m^{f/f}$ homozygotes whose IgG1 concentration had been carefully measured with radial immunodiffusion.

Dilution series of newborn samples were prepared in gelatin-PBS-Tween throughout the experiments, but samples taken at 4 or 6 months were first diluted 1/10 into 10% adult serum of the same Gm genotype as the child. This led to a situation where the concentration of normal human serum was approximately equal in the critical tubes regardless of the age of the child. No evidence was obtained that this precaution was necessary, but it was undertaken nevertheless.

Quantitation of a-Positive IgG1. The method was identical to the one used for f quantitation except that a-positive IgG1 was used for the coating of the plates, and the mAb was anti-G1m(a) [5E7 (ref. 23), diluted 1/400,000]. The method was not used in the main experiment.

Isotype- or Allotype-Specific Quantitation of Anti-Tetanus Toxoid Antibodies. A four-layer solid-phase radioimmunoassay (RIA) was used as in Reference 24. Tubes were first coated with the antigen, then with human serum dilutions. The third reagent was a monoclonal antibody (mAb) specific for IgG1 or its allotype; the fourth, a radioactive rabbit anti-mouse Ig antibody. The mAb for IgG1 was 2C7 (HP 6070) (24), and it was produced locally. Anti-f (5F10) and anti-a (5F7) reagents have been described above.

Polystyrene tubes were coated with 0.5 ml of tetanus toxoid (Public Health Institute, Helsinki; 10 μg/ml). After overnight incubation at 4°C, the tubes were washed and postcoated with 0.6 ml of 0.5% bovine serum albumin (BSA) at room temperature for 4 hr. The tubes were washed three times, and serial dilutions of human serum (0.4 ml) were added. After an overnight incubation at 4°C, the tubes were washed and the mAb was added. The working dilutions of the mAb (ascites fluids) were 1/300 for 2C7, 1/10,000 for anti-f, and 1/3000 for anti-a. The volume was 0.3 ml. The tubes were incubated overnight at 4°C and washed three times. ^{125}I-Labeled affinity-purified rabbit anti-mouse antibody was added, and the tubes were incubated at 4°C overnight, washed three times, and counted. Serum dilutions (1/100, 1/200, 1/400, 1/800, 1/1600, 1/3200, 1/6400, 1/12,000, and 1/24,000) were tested with anti-IgG1, anti-a, or anti-f.

Table II. Specificity of Inhibition Assay for f-Positive or a-Positive IgG1[a]

	Titer in	
	a assay (5E7)	f assay (5F10)
$G1m^{a/a}$ homozygote serum tested		
Conventionally	960	<10
In the presence of 1% f/f serum	850	n.t.
In the presence of 10% f/f serum	300	n.t.
$G1m^{f/f}$ homozygote serum tested		
Conventionally	<10	1430
In the presence of 1% a/a serum	n.t.	1570
In the presence of 10% a/a serum	n.t.	1330

[a]Effect of an excess of the opposite allotype on quantitation of allotypes a and f by the inhibition assay. n.t., not tested.

RESULTS

Specificity of the Method

Quantitation of f-positive or a-positive IgG1 was carried out in the presence of an artificial excess of the opposite allotype because such an excess might be present in the test situation. The a assay was specific in that an $G1m^{a/a}$ homozygote serum inhibited to a high titer, but an $G1m^{f/f}$ homozygote serum did not (Table II). However, the presence of 1 or 10% f/f serum had a distinct effect on the inhibition titre of the a/a serum. The f assay was specific throughout the experiments. An a/a serum did not inhibit in the test, and its presence did not interfere in the quantitation of f-positive IgG1 (Table II). On the basis of these tests, we concluded that maternal f-positive IgG1 can be quantitated in $G1m^{a/a}$ children, but we did not have a satisfactory anti-G1m(a) antibody for the reverse situation. Only f-positive IgG1 was quantitated in the main experiment.

The other method for the survival study was quantitation of maternal tetanus toxoid antibodies in the child. The anti-f enhanced assay was very specific again (Table III). The anti-a enhanced assay was only 10 times more efficient in developing a-positive than f-positive IgG1 antibodies (Table III). However, because no excess of one allotype over the other was expected in the antibody test, we decided to apply both antiallotype antibodies in anti-tetanus toxoid quantitation.

Decay of Maternal f-Positive IgG1 in Young Infants

Nine infants were studied. All were genetically $G1m^{a/a}$ homozygotes as determined from the sample

Table III. Specificity of Antibodies 5E7 [Anti-G1m(a)] and 5F10 [Anti-G1m(f)] as Developing Agents in Solid-Phase Anti-Tetanus Toxoid Assay[a]

Donor	Allotype	Titer with anti-IgG1	Titer with anti-a	Efficiency relative to anti-IgG1	Titer with anti-f	Efficiency relative to anti-IgG1
1	f/f	49,000	13,000	0.265	44,000	0.898
2	f/f	16,000	3,300	0.206	18,000	1.125
Average				0.236		1.06
3	a/a	12,000	29,000	2.42	<100	<0.0083
4	a/a	18,000	43,000	2.39	<100	<0.0055
Average				2.40		<0.0069
"Specificity"				10.2-fold		>153-fold

[a]Four recently immunized medical students, two $G1m^{f/f}$ and two $G1m^{a/a}$, were tested.

taken at the age of 14 months. Three serum samples per child were tested for maternal IgG1, one taken at the age of 1–3 days, the second between day 118 and day 124, and the third between day 180 and day 188. The three samples from one child were always tested in one session. Each series of three samples was tested in three different sessions. The average proportion residing in the circulation of an infant at ages ca. 4 and 6 months was calculated from the three values (percentage of concentration in newborn sample). The concentrations were approximately 10 and 3% of the newborn concentration at ages 4 and 6 months, respectively (Table IV). The growth of the child had caused irrelevant dilution, and to obtain the surviving fraction of the maternal immunoglobulin, a correction was conducted based on average growth curves of girls and boys in Finland (25). The surviving fractions were 17 and 6.9% on the average at ages 4 and 6 months, respectively (Table IV).

From these proportions the half-lives were calculated (Table IV). The average values for the nine children were 47 days for the first 4 months and 48 days for the next 2 months. The average half-life for the whole 6 months was 47 days.

In some cases the half-life seems to change from the period 0–4 months to the period 4–6 months (children 161 and 168). An error in the quantitations of f-positive IgG1 in the 4-month sample is probably one reason for this apparent change. The observed half-life for the entire 6-month period was not exceptional in these two children (42 days).

Decay of Maternal Anti-Tetanus Antibody

Only eight newborn samples had enough maternal antibodies to permit the measurement of the half-life. Two were $G1m^{a/a}$ and six $G1m^{f/f}$ homozygotes. The average half-life for the f-positive anti-

Table IV. Decay of f-Positive (Maternal) IgG1 in $G1m^{a/a}$ Homozygotes During the First 6 Months of Life[a]

Child No., sex	Three first samples taken at ages (days)	Concentration of maternal f-positive IgG1 in first sample (g/L)	Concentration of maternal IgG1 at age ca. 4 mo (% of newborn conc.)		Concentration of maternal IgG1 at age ca. 6 mo (% of newborn conc.)		Half-life (days)	
			Uncorrected average	Corrected for weight increase	Uncorrected average	Corrected for weight increase	0–4 mo	4–6 mo
104 f	3, 121, 182	2.4	9.34	17.1	2.33	4.99	46	34
106 f	2, 119, 180	2.1	11.70	21.1	3.40	7.17	52	39
111 f	2, 118, 181	2.8	10.20	18.2	3.38	7.23	47	47
113 f	2, 122, 180	2.0	8.40	15.1	3.49	7.36	44	56
116 m	2, 122, 188	2.9	9.51	18.3	3.88	8.73	49	62
146 m	1, 126, 187	2.5	9.78	19.1	3.78	8.51	52	52
161 f	1, 121, 180	2.3	9.60	17.6	2.56	5.40	48	35
164 m	2, 121, 180	2.1	9.23	16.9	3.45	7.28	46	49
168 m	3, 124, 182	3.4	5.70	10.9	2.36	5.24	38	55
Mean			9.27	17.1	3.18	6.88	46.9	47.7

[a]Values given are arithmetic means of three determinations. The average day-to-day variation of the percentages (variation analysis) was 23% at 4 months and 26% at 6 months. This means that 95% confidence limits of the averages given are ca. 25% below and above the percentage given.

Table V. Decay of Maternal Tetanus Toxoid Antibody in the Child[a]

Child No., sex	Samples taken at ages (days)	Tetanus toxoid antibody titer (maternal) at age 1–3 days	Maternal antibody titer at age 116–130 days (% of newborn titer)	Survival percentage corrected for weight increase of child	Half-life
03 f	3, 130	3,430	11.30	21.0	56
07 f	1, 123	2,402	7.70	14.1	43
04 m	1, 127	4,096	9.30	18.9	52
10 f	2, 122	4,023	9.39	17.4	48
11 m	1, 126	5,992	8.36	16.4	48
14 m	1, 125	14,000	8.04	15.8	47
51 f	1, 116	3,117	11.01	20.1	50
77 f	1, 123	12,800	12.50	22.9	57
Mean					50.1

[a]Children 03 and 07 are f-negative homozygotes, and f-positive antibody was monitored. All other children were a-negative homozygotes, and a-positive antibody was monitored.

body was 49 days, and that for the a-positive 50 days (Table V). These values were not significantly different from each other or the mean half-life that was measured for f-positive IgG1 by the inhibition method.

As mentioned above, the anti-a allotype reagent used was not fully specific. For this reason the survival values presented for a-positive anti-tetanus toxoid antibody in Table V are somewhat uncertain. However, the fact that the observed half-life for the a-positive IgG1 (49 days) was virtually the same as the half-life (47 or 50 days) determined for f-positive IgG1 suggests that the observed value is correct.

Concentration of Endogenous Immunoglobulin IgG1 in Cord Blood Serum

Since quantitation of f-positive IgG1 was specific and sensitive, we decided to determine the concentration of endogenous IgG1 in the cord blood of newborn babies. We obtained 75 pairs of mother-cord blood samples and allotyped the mothers. Thirteen $G1m^{a/a}$ homozygote mothers were found. IgG1 and f-positive IgG1 were then quantitated from the 13 cord blood serum samples. The concentrations of IgG1 in the 13 maternal samples were also determined.

Concentrations of IgG1 in cord blood samples varied from 4.2 to 8.4 g/L (mean, 6.63), and those of maternal sera from 3.9 to 6.7 g/L (mean, 4.73). Cord sera had 4–97% (mean 40%) higher concentrations than the maternal serum.

Measured concentrations of f-positive IgG1 in most cord blood serum samples varied from 2 to 13 mg/L. It was less than 2 mg/L in five samples including two that had less than 0.5 mg/L (Fig. 1).

The scatter of values does not exhibit two clearcut groups as should have been expected [on the basis of gene frequencies in Finland, five babies were expected to be $G1m^{a/a}$ homozygotes and eight $G1m^{f/a}$ heterozygotes (26)]. For this reason and

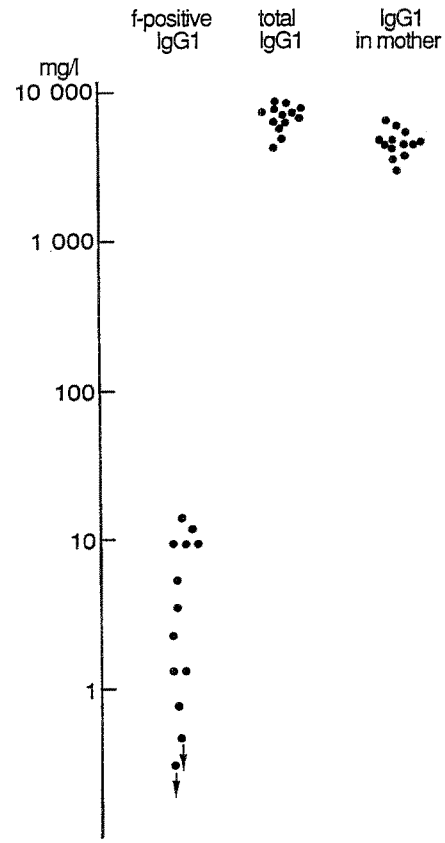

Fig. 1. Concentration of f-positive and total IgG1 in the cord blood sera of 13 children. Also, the total IgG1 serum concentration of their f-negative mothers is given.

because the samples had about a thousand times more a-positive than f-positive IgG1, the possibility must be considered that a-positive IgG1 erroneously increased the measured concentrations of f-positive IgG1; the values must therefore be taken as upper limits of endogenous f-positive IgG1.

DISCUSSION

Our data support the view that IgG molecules undergo a decay in the circulation with a first-order kinetics. The calculated half-life for maternal IgG1 in the infant's circulation was ca. 47 days for both the first 4 months and the following 2 months. The mean value was the same for the total f-positive IgG1 and for anti-tetanus antibodies of G1m(a) or G1m(f). Individual half-life values varied from 34 to 57 days; this variation may be due to inaccuracy of the techniques. Another possibility is that the half-life really is different in different individuals. The sizes of the serum samples did not permit us to repeat determinations so many times that an answer had been obtained. The data suggest that the same half-life of ca. 7 weeks is valid for both main allotypes of IgG1. By pooling all data for the period of the first 4 months, we obtained an average half-life of 48.4 days.

It has been found that IgG1 and IgG2 have identical residence times in circulation (1–3). Since they account for more than 80% of the total IgG and since the half-life of IgG3 is shorter, the average half-life for the whole IgG must be approximately the same as the half-life of IgG1. Nonetheless, most reported half-lives for IgG or IgG1 (Table I) are different from the one we found, and an explanation is needed.

Some earlier investigators used iodine-labeled IgG, and the half-life values obtained (12–23 days) were shorter than what we found. The difference between the mean half-life of 48 days reported here and the shorter half-lives for iodine-labeled IgG found by others (1–4) might be explained by the immunoglobulin molecules being damaged in the iodination procedure. Another possible explanation is that the half-life is twice as long in newborn babies as in adults, but that seems unlikely.

Most earlier investigators who have measured unlabeled IgG have reported half-lives as long as or longer than the one we observed (Table I). Typically, in several earlier studies, a great scatter of values in different individuals has been found. The earlier studies were based on the assumption that the IgG measured was totally foreign (either intravenous commercial IgG or maternal antibody). This was often an incorrect assumption. In several cord blood samples, endogenous IgG1 accounted for ca. 0.2% of all IgG1 (Fig. 1). This proportion increases with age. Even a small endogenous contribution would have had a considerable effect on half-lives of Table I because only few samples per individual were studied, and the concentration in the later samples had a great effect on the calculated half-life. Endogenous synthesis may explain both some surprisingly long half-lives (96 days) and the great interindividual variation observed (7–21). Intrinsic synthesis cannot account for the fact that half-lives observed in immunodeficient children were usually shorter than those observed in this study. The cause of this difference is unknown, but it might have been caused by the process of preparation of the commercial γ-globulins. Another possibility is that because these patients were ill, they catabolized IgG more rapidly than healthy children.

Two kinds of factors might have complicated our study but appear not to have done so. One was concentration-dependent variations in the half-life (2). The concentration of IgG varied from a high newborn value to a low value at 4 months and a higher value again at 6 months. If the half-life really is dependent on the concentration of IgG, the variations in the first 6 months of life look too small to have a visible effect. The other complicating factor might have been antiallotype antibodies developed by the child (26). They might have shortened the half-life of maternal IgG1 during the last 2 months of observation. No such shortening was seen.

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