Turnover rate of anti-D IgG injected during pregnancy

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Abstract

Anti-D IgG was injected into 15 Rh-negative women in the 28th week of gestation and into three non-pregnant women. The uptake of anti-D after the intramuscular injections was calculated by measuring the concentration of antibody in the plasma with an autoanalyser. The biological half life and the catabolic rate of anti-D IgG were calculated according to a compartmental model. The recovery in vivo of anti-D IgG was on average 24% in the non-pregnant women and 21% in the pregnant women. The half lives of anti-D IgG were 24 and 21 days, respectively. With a dose of 125 µg the plasma anti-D concentration was less than 1 ng/ml at about 10 weeks after the injection. With double the dose the concentration at delivery was at least 1 ng/ml.

Although 250 µg of anti-D IgG seems to be effective when given in the 28th week of gestation, the great individual variations in uptake and recovery rates will lead to occasional cases of Rh-immunisation during pregnancy despite all routine regimens.

Introduction

There is good evidence that giving anti-D immunoglobulin both antenatally and at delivery has substantially reduced the incidence of Rh-immunisation.¹⁻³ Moreover, when antenatal treatment with anti-D IgG is indicated a single dose of 250 µg in the 28th week of gestation is effective. A smaller dose and a different timing may be just as adequate and more economical but have not been tried.

Since there is almost no information available on the biological half life of anti-D IgG, which determines the effectiveness of different dose-schedules, we studied this question in pregnant and non-pregnant women.

Subjects and methods

Fifteen Rh-negative pregnant women were given anti-D IgG intramuscularly at 28 weeks' gestation. The doses were 125 µg in eight and 250 µg in seven of the women. Three non-pregnant Rh-negative women were given the smaller dose. The anti-D IgG preparation (Rhesonativ) used was fractionated by a modified cold ethanol method by Kabi Ab, Stockholm, Sweden. The anti-D content of this preparation was determined by the direct method of Hughes-Jones and Stevenson.⁴ The aim and scope of the study were carefully explained to the women.

Blood samples from the pregnant women were drawn before and 1, 2, 3, 5, 7, 9, and 11 weeks after the injection and at delivery. In the three non-pregnant women the first postinjection sample was taken three days after the injection followed by samples at the same intervals

as above and an additional sample 12 weeks after the injection. The plasma samples were frozen immediately at -20°C and analysed in series.

ABO and Rh grouping was done on all the women and their newborn infants. The women who delivered Rh-positive infants were given 250 µg of anti-D IgG within 24 hours of delivery.

Anti-D was measured in the plasma samples by the AutoAnalyzer method.⁵ The lowest plasma concentration of anti-D which could be reliably detected with this method was 1 ng/ml. The plasma volume was estimated to be 45 ml/kg body weight for non-pregnant women and 50 ml/kg for pregnant women.⁶ The biological half life was calculated by the method of residuals, the usual technique for resolving a curve into its various exponential components.⁷ The recovery in vivo of the injected anti-D IgG was calculated using the formula

$$\frac{100 \times \text{plasma volume (ml/kg)} \times \text{body weight} \times \text{peak value of anti-D}}{\text{injected dose of anti-D IgG}}$$

Results

The biological half life of anti-D IgG after an intramuscular injection of 125 µg in the three non-pregnant women was 23.9 days. The maximum concentration was reached after seven days. Anti-D was no longer detectable a mean of $92.7 \pm (1 \text{ SD}) 4.8$ days after the injection (table I).

Of the eight pregnant women given 125 µg of anti-D IgG, three were delivered of Rh-negative infants. The biological half lives of anti-D IgG in two of these women were 16.2 and 21.3 days. In the third we could not calculate the half life owing to the very low uptake of the injected anti-D IgG. The maximum concentrations of anti-D in the first two women were 8.0 ng/ml and 9.0 ng/ml. In the third it was only 2.9 ng/ml. The concentration of anti-D reached the plasma level of 1 ng/ml a mean of 66 ± 4.7 days after the injection.

The mean half life of anti-D IgG in four of the five women who received 125 µg anti-D IgG and who delivered Rh-positive infants was 21.7 days. The maximum concentrations were 5.7, 5.8, 8.8, and 11.6 ng/ml, and the anti-D was no longer detectable 71.4 ± 10.0 days after the injection. In the fifth woman the highest level was only 2.2 ng/ml. The concentration of anti-D was less than 1 ng/ml after 21 days, which did not permit an accurate calculation of the half life (table I).

Three of the seven women who received 250 µg of anti-D IgG were delivered of an Rh-negative infant. Their mean half life of anti-D was 23.4 days. The maximum concentration was 15.0 ng/ml. The corresponding figures for the four women delivered of an Rh-positive infant were 19.5 days and 17.1 ng/ml (table II).

The mean value ($\pm 1 \text{ SD}$) for the time of the lowest detectable concentration of anti-D was 118.0 ± 6.8 days in the women with Rh-negative infants and 119.7 ± 14.8 days in those with Rh-positive infants.

When the two women with very low maximum concentrations were excluded, the mean recovery in vivo of anti-D IgG was 24% (23-27) in the non-pregnant women and 21% (14-32) in the pregnant women (table III).

Discussion

The average biological half life of normal IgG has been estimated from turnover studies with ¹²⁵I-labelled human gammaglobulin to be 23 days.^{8,9} Our study shows clearly that the half life of anti-D IgG measured by specific antibody activity is no different from that of normal IgG—that is, 24 days in non-pregnant women and 21 days in pregnant Rh-negative women. As might be expected, the figure for the non-pregnant women was closely comparable with the value obtained in Rh-negative male volunteers.¹⁰ The lower mean value in the pregnant women reflects the well-documented transfer of 10-15% of the antibody across the placenta into the fetal circulation.

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Smith *et al* found that the concentration of anti-D IgG reached its maximum two to four days after the intramuscular injection, corresponding to an average of 40% of the injected dose.¹⁰ Jouvenceaux reported almost the same recovery in vivo, but five to 10 days after the injection.¹¹ In our study the recovery rates were estimated to be 23-27% in the non-pregnant women and 14-32% in the pregnant women (excluding two patients who had a very low uptake of the injected doses).

In the woman with low anti-D concentrations who delivered an Rh-positive infant there may have been increased consumption of the injected antibody due to transplacental haemorrhages from the Rh-positive fetus. Local loss of intramuscularly injected gammaglobulin has been recorded in earlier studies, but the precise mechanism is not well documented.^{12 13} Furthermore, it has been suggested that, for example, muscular activity may influence the extent of the resorption of the injected dose.^{9 14}

negative women. Our results show that with a single dose of 125 µg at the 28th week of gestation the plasma concentration was less than 1 ng/ml about 10 weeks after the injection. This dose is therefore insufficient if the suppression of Rh-immunisation during pregnancy depends on the presence of measurable amounts of anti-D IgG in the plasma at delivery.

A schedule based on a single dose of 250 µg of anti-D IgG in the 28th week, however, gave a plasma concentration of anti-D of at least 1 ng/ml at delivery, which is probably enough for the purpose. There were no significant differences in the mean time of the lowest detectable plasma concentrations of anti-D between women who delivered Rh-negative infants and those who delivered Rh-positive infants. The striking individual variations in both uptake and recovery rates combined with the eventual consumption of the injected antibody during pregnancy will be responsible for occasional cases of Rh-immunisation during pregnancy despite routine use of anti-D IgG antenatally.

TABLE I—Biological half life and maximum and minimum detectable plasma concentrations of anti-D IgG after intramuscular injection of 125 µg of anti-D immunoglobulin in three non-pregnant and eight pregnant women at 28 weeks' gestation

Rh-negative women	No of women	Weight (kg)	Biological half life (days)	Maximum concentration (ng/ml)*	Mean No (± 1 SD) of days after injection when value fell below <1.0 ng/ml
Non-pregnant	3	62 (52-67)	23.9 (18.0-29.2)	11.0 (9.6-12.4)	92.7 ± 4.8
Pregnant, Rh-negative infants	3	62 (49-70)	18.8 (16.2-21.3)	8.5 (8.0-9.0)	66.7 ± 4.7
Pregnant, Rh-positive infants	5	65 (59-74)	21.7 (17.9-23.7)	8.0 (5.8-11.6)	71.4 ± 10.0

*Maximum anti-D concentrations in one woman who delivered an Rh-negative infant (2.8 ng/ml) and one who delivered an Rh-positive infant (2.2 ng/ml) are not included.

TABLE II—Biological half life and maximum and minimum detectable plasma concentration of anti-D IgG after intramuscular injection of 250 µg of anti-D immunoglobulin in seven pregnant women at 28 weeks' gestation

Rh-negative women giving birth to	No of women	Weight (kg)	Biological half life (days)	Maximum anti-D concentration (ng/ml)	Mean No (± 1 SD) of days after injection when value fell <1.0 ng/ml
Rh-negative infants	3	66 (64-66)	23.4 (17.8-29.6)	15.0 (13.3-17.5)	118.0 ± 6.8
Rh-positive infants	4	68 (65-73)	19.5 (16.6-24.2)	17.1 (10.8-23.0)	119.7 ± 14.8

TABLE III—Recovery in vivo of anti-D IgG in 17 women expressed as percentage of injected dose

Rh-negative women	No of women	Mean recovery in vivo (range) (%)
125 µg anti-D:		
Non-pregnant	3	24 (23-27)
Pregnant, Rh-negative infants*	3	20 (16-25)
Pregnant, Rh-positive infants	5	20 (16-26)
250 µg anti-D:		
Pregnant, Rh-negative infants	3	20 (17-23)
Pregnant, Rh-positive infants	4	24 (14-32)

*Recovery of anti-D IgG in one woman was only 8% and is not included.

There is no reason to believe that the lower recovery rates in our series were due to the fact that we did not measure plasma concentrations in the first six days after the injection of anti-D IgG in the pregnant women, because in the three non-pregnant women the highest plasma value was found on the 7th and not on the 3rd day. Nevertheless, there is a report of two patients injected with radiolabelled gammaglobulin in whom the recovery rate was about 32% on the 5th day and 20% on the 7th day after the injection.⁹

Apart from that, our study shows large variations in the recovery rates and the biological half lives of anti-D IgG between the women, which are probably much more important than differences between absolute values.

One of the main purposes of this study was to evaluate the optimal dose of anti-D IgG for antenatal treatment of Rh-

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