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Immunosuppressive Therapy in Rh-incompatible Transfusion

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Postpartum injections of 250 μ g of anti-D gammaglobulin prevent Rh-immunization of Rh-negative women, with an immunosuppression success rate of approximately 95% (Eklund and Nevanlinna, 1971).

The average fetomaternal transfusion, however, is less than 1.5 ml in 98% of cases (Clarke *et al.*, 1966), and so far there are few observations on trying to suppress primary Rh-immunization due to massive inadvertent transfusion of Rh-positive blood (Hughes-Jones and Mollison, 1968; Keith *et al.*, 1970).

We report here three cases in which Rh-negative women received in error a Rh-transfusion and in which large doses of anti-D gammaglobulin appeared to have suppressed primary immunization when they were tested for immune anti-D formation 12 months or later after the accident.

Case Reports

Case 1.—A 22-year-old primigravida was delivered of a child by caesarean section on 8 March 1968. She was group A Rh-negative and the infant's group was A Rh-positive. A transfusion of 400 ml of A Rh-positive blood was given on 12 March. Five hours later an infusion of anti-D plasma was started intravenously and given in the course of 31 hours. After the infusion of 180 ml over two hours the patient's temperature rose to 38.6°C and she had an attack of shivering. The treatment was stopped for 14 hours and started again at a rate of 30 ml/hour without further reactions. A total of 630 ml of plasma was administered, containing 8,200 μ g of anti-D (see Table), as estimated by Dr. N. C. Hughes-Jones. The plasma haemoglobin reached a peak concentration of 150 mg/100 ml. The urinary output was normal throughout. The number of surviving Rh-positive cells was determined by the Ashby differential agglutination technique; the results are shown in the Chart. Samples of blood obtained up to 22 months after the transfusion showed no antibody. At the time of writing the patient had not had a subsequent Rh-positive pregnancy.

Case 2.—An 18-year-old woman aborted at 16 weeks' gestation on 21 May 1969. She had not been pregnant before and had never received blood transfusions. Because of severe bleeding she was given 800 ml of A Rh-positive blood. She was group A Rh-negative. Nine hours after the beginning of the blood transfusion she was given 2,500 μ g of anti-D gammaglobulin, and 24 hours later she received an additional dose of 2,500 μ g (see Table). Approximate estimates of the survival of transfused red cells were made by an Ashby count; the results are shown in the Chart. On 16 December 1970, 19 months after the transfusion, she gave birth to an O Rh-positive child. Tests for antibody during pregnancy and at the delivery were all negative.

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Case 3.—A 21-year-old woman gave birth to her first infant on 27 February 1969. She had not been pregnant before, nor had she required a blood transfusion. Between the second and fifth postpartum hours a transfusion of 400 ml of AB Rh-positive blood was given. Her blood type was AB Rh-negative and her infant's type was AB Rh-positive. Twelve hours later she was given 1,500 μ g of anti-D gammaglobulin, followed by a further 1,200 μ g at 12-hour intervals. A total of 3,900 μ g of anti-D was administered (see Table). Blood samples taken several times up to 12 months after delivery were free of antibody. The patient had not become pregnant as of March 1971.

Estimated survival of Rh-positive red cells in Cases 1 and 2.

Comment

The value of immunosuppressive therapy with anti-D gammaglobulin depends on a knowledge of the risk of immunization resulting from the Rh-incompatible transfusion involved. It has been postulated that a single transfusion of Rh-positive blood stimulates anti-D antibody formation in at least half the subjects (Mollison, 1967). But it appears that if a Rh-negative woman has been transfused with Rh-positive blood a subsequent Rh-positive pregnancy in most cases provokes secondary immune response (Nevanlinna, 1953).

Rh-incompatible large transfusions have been successfully treated in four out of five cases, three of which are presented here (see Table). Though it is not known which of the actual recipients would have been immunized, since only one of them subsequently delivered a Rh-positive child, we have the impression that the rate of immunization must be much higher than one out of five. However, it is possible that a later exposure to the Rh-antigen will still induce a secondary response in the remaining subjects. It is not known how long a delay in the administration of anti-D gammaglobulin is permissible before the possibility of preventing Rh-immunization is missed. There is evidence that anti-D gammaglobulin is effective when giving as late as 72 hours after an injection of Rh-positive cells (Pollack *et al.*, 1969). In all five cases treatment started not more than three days after the transfusion accident.

The disappearance time of Rh-positive cells in Case 1 treated with anti-D plasma was about one day. In Case 2 complete clearance took 6-7 days. The same rate was reported by Keith *et al.* (1970) in one case in which anti-D also did not form. Ninety-five per cent. clearance of Rh-positive cells occurred after 10 days in a case recorded by Hughes-Jones and Mollison (1968), in which the anti-D gammaglobulin failed to prevent

Details of Five Cases of Massive Rh-incompatible Transfusion treated with Anti-D Gammaglobulin

Authors	Case No.	Rh-positive Red Cells Transfused (ml)	Anti-D (μ g) Administered	100% Clearance (Days after Transfusion)	Antibody-Antigen Ratio (μ g:ml)	Test for Anti-D Formation	
						Time of Testing after Transfusion (Months)	Result
Hughes-Jones and Mollison (1968)	1	400	1,000 i.m.	12	2.5:1	3½	Positive
Keith <i>et al.</i> (1970)	1	400	17,700 i.m.	6-7	44:1	8	Negative
Present series	1	160	8,200 i.v.	1-2	51:1	22	Negative
	2	320	5,000 i.m.	6-7	16:1	19	Negative
	3	160	3,900 i.m.	?	25:1	12	Negative

primary immunization. The ratio of antibody to antigen in Case 1 was 51 to 1 and in Case 2 and 3 it was 16 to 1 and 25 to 1 respectively. The corresponding ratio in the case reported by Keith *et al.* was 44 to 1, and in that of Hughes-Jones and Mollison 2.5 to 1. These observations suggest that a more accelerated red cell destruction occurs when anti-D is administered intravenously. If a rapid clearance of Rh-positive cells is a real advantage this approach might be of considerable value.

No adverse reactions were noted in the cases treated with anti-D gammaglobulin, but the patient who received anti-D plasma developed signs of a mild transfusion reaction.

Hughes-Jones and Mollison (1968) pointed out that treatment of a large volume of mistransfused Rh-positive blood would require about 10,000 μ g of anti-D for 400 ml of Rh-positive red cells. In contrast Keith *et al.* (1970) recommended a dose of at least 300 μ g of immunoglobulin, as originally suggested by Pollack *et al.* (1969), for each 10 ml of Rh-positive blood given, which corresponds approximately to 4 ml of red cells.

Though there seems to be no danger of an excess of anti-D and apparently no distinct risk of renal damage even when large amounts of Rh-positive cells are rapidly destroyed, our experience favours the more cautious approach suggested by Hughes-Jones and Mollison (1968). A reasonable therapeutic

regimen would be not more than 1,000 μ g for every 40 ml of Rh-positive red cells in divided doses. During the course of the treatment the patient's response should be carefully monitored so that the dose of anti-D gammaglobulin can be modified as required.

It is to be expected that most Rh-negative women become immunized following exposure to massive transfusion of Rh-positive blood, and for the present every fertile Rh-negative recipient must be considered at risk and should be immediately treated with adequate doses of anti-D gammaglobulin.

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