

Case report

Urticaria from allergy to a purified human anti-Rh antibody preparation

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This case presentation describes a young woman who developed generalized urticaria after receiving the human anti-RhD(D) preparation, WinRho, intravenously. Allergy skin tests and the radioallergosorbent test (RAST) for IgE antibodies to the human anti-D immunoglobulin preparation were positive. Further studies using high-pressure liquid chromatography and protein A column chromatography implicated a nonimmunoglobulin low-molecular-weight contaminant. This case report illustrates an allergic reaction to a highly purified human immunoglobulin preparation, and demonstrates approaches to assessment of such a reaction.

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Passive immunization of Rh-negative women with antibodies to RhD has greatly decreased the risk of Rh isoimmunization and erythroblastosis fetalis. Commercial preparations formerly used were high-titer anti-D human plasma. These have been replaced by highly purified anti-D immune globulin preparations. A widely used example is WinRho, given intravenously and prepared in Winnipeg, Canada, by Rh Pharmaceuticals, Inc through fractionation of hyperimmune human plasma by ion exchange with DEAE-Sephadex (5).

Adverse reactions to various types of human immunoglobulin preparations are not uncommon. These reactions are presumably mediated through the high content of IgG aggregates or IgA (2-4, 7). The latter can be dependent upon IgE-antibodies to IgA, especially in hypogammaglobulinemia. The anti-D immunoglobulin, WinRho, compares favorably with other human immunoglobulin preparations in this regard.

Immunoelectrophoresis and double-immunodiffusion have shown that the anti-D immunoglobulin is a highly purified IgG preparation with IgA content less than 2 µg per 2.5-ml vial. Furthermore, the content of IgG aggregates and anticomplementary activity is very low (5, 6).

This case report describes an allergic reaction to WinRho, a highly purified human immunoglobulin preparation in an immunocompetent host.

Case report

A 26-year-old woman received 120 µg of the human anti-D immunoglobulin preparation intravenously 3 days after delivery of a second child. On the following day, she developed generalized urticaria; there were no other features of a systemic reaction. The urticarial lesions occurred randomly on the body and were transient, disappearing in minutes or hours. There was no angioedema. No laboratory tests were done at the onset of the urticaria. The urticaria persisted but gradually subsided over 5 months under treatment with antihistamines and occasional prednisone. Several years earlier, the patient had received an anti-D immunoglobulin preparation after the birth of her first child, and had tolerated it well. There was no past history of allergy or adverse drug reaction and no past history of other pregnancies. The patient did not receive any unusual drug treatment during or after delivery.

Ten months after the onset of urticaria, allergy skin tests by the prick and intradermal methods were

performed with WinRho and an alternate anti-D preparation HypRho-D (Miles Inc, USA). The tests with both preparations were positive, with wheal and flare, and intense itching within a few minutes. Positive skin tests were maximal at 10 and 20 min with the prick and intradermal methods, respectively. Skin tests with WinRho and HypRho-D were negative in two healthy men who served as control subjects. Normal saline in which anti-D immunoglobulin preparation is dissolved had been used as negative control for all skin tests. These tests were negative in the patient as well as in healthy subjects. A control (histamine, 10 mg/ml) epicutaneous test was positive.

Special studies

As a test for serum IgE-antibodies to the anti-D immunoglobulin preparation, WinRho, a radioallergosorbent test (RAST) was performed. The result (% binding) was positive in the patient (11%) as compared with the control sera of two healthy, non-allergic people (mean = 4.1%) and six people with ragweed hay fever (mean ± standard deviation = 3.8 ± 0.28%) (Table 1). To explore the specificity of the RAST to the anti-D immunoglobulin

preparation, we performed a RAST-inhibition (blocking) experiment. WinRho was incubated with the serum of the patient and the sera of ragweed-allergic subjects and corresponding RAST was performed; WinRho blocked the WinRho RAST, but not the ragweed RAST. Likewise, ragweed allergen incubated with the sera of ragweed-allergic subjects or the serum of the patient blocked the ragweed RAST, but not the WinRho RAST.

To examine the possibility that the IgE antibodies to the anti-D immunoglobulin preparation could be reacting with IgG-idiotypic, we performed an anti-D immunoglobulin RAST blocking experiment with another human immunoglobulin preparation, hepatitis B immunoglobulin (HyperHep, Miles, Inc, USA), as well as the WinRho. The hepatitis B immunoglobulin blocked the anti-D immunoglobulin RAST performed with the patient's serum, but it did not block a ragweed RAST performed with sera of ragweed-allergic subjects (Table 1). We concluded that the IgE antibodies in the patient's serum did not have anti-D idiotype specificity.

The anti-D immunoglobulin preparation was fractionated by high-pressure liquid chromatography (HPLC). The resulting fractions were used in a WinRho RAST blocking test. In addition, WinRho was fractionated by protein A column chromatography, which separates IgG from non-IgG components, and the resulting fractions were also tested by the WinRho RAST blocking test. In both experiments, the blocking activity did not correspond to the IgG fractions. An HPLC fraction with a molecular weight lower than IgG was most potent in blocking the anti-D immunoglobulin RAST. The non-IgG fraction from the protein A chromatography was 10 times more active than the IgG fraction in blocking the WinRho RAST. Results of *in vivo* and *in vitro* studies are summarized in Table 1.

Discussion

The anti-D immunoglobulin preparation, WinRho, is a highly purified IgG product from human serum with an excellent record of efficacy and safety (1). Apparently, this is the first reaction to this preparation in which allergy has been documented: a literature search was performed using Medline from 1970 through June of 1995. However, a case of anaphylactoid reaction to another anti-D immunoglobulin preparation has been described in a patient who had negative skin tests to the preparation (8). In regard to WinRho, we are also aware of mild skin adverse reactions after its use in an additional four patients that have been reported to the manufacturer (Wolowski BMR, personal communication).

The occurrence of urticaria within 24 h after the injection of WinRho would be consistent with the

Table 1. Summary of special studies

Identification of IgE-antibodies to anti-D immunoglobulin	
1. Allergy skin tests	● Prick and intradermal test in the patient: strongly positive ● Prick test in two healthy control men: negative
2. Anti-D immunoglobulin RAST (% binding of ¹²⁵ I-labeled anti-IgE)	● Patient: 11% ● Ragweed-allergic patients: 3.8±0.28% (M±SD, n=6) ● Healthy controls: 4.1% (M, n=2)
RAST-inhibition (%) to confirm specificity of IgE-antibodies to anti-D immunoglobulin	
1. Anti-D immunoglobulin RAST with patient's serum	● Inhibition with anti-D immunoglobulin: 84% ● Inhibition with hepatitis B immunoglobulin: 64% ● Inhibition with ragweed: 12%
2. Ragweed RAST with serum of ragweed-allergic controls	● Inhibition with ragweed: 71% ● Inhibition with anti-D immunoglobulin: 0% ● Inhibition with hepatitis B immunoglobulin: 1%
RAST inhibition (%) to identify antigenic specificity of IgE antibodies to anti-D immunoglobulin	
Anti-D immunoglobulin RAST with patient's serum: inhibition by anti-D immunoglobulin fractions	
1. From protein A column	● Inhibition with non-IgG fraction more than with IgG fraction: 80% vs 8%
2. From HPLC	● Inhibition by fraction with mol. wt. lower than IgG more than with IgG fraction: 70% vs 11%

conclusion that it was initiated by the preparation. The demonstration of a positive allergy skin test in the patient, but not in the control subjects, and the demonstration of the serum IgE-antibodies to the anti-D immunoglobulin preparation are further evidence of allergy to this biologic product. The Win-Rho specificity of the IgE-antibodies is supported by selective results of the WinRho and ragweed RAST inhibition tests outlined in Table 1.

The IgE antibody in the patient's serum reacted with a component of the anti-D immunoglobulin with a molecular weight lower than IgG. Thus, the allergic reaction seems to have been due to a contaminant which was copurified with IgG in a small amount during production. Since the antigenic contaminant was not characterized, we do not know whether this molecule has been found to elicit autoimmune or isoimmune responses. Although the antigenic reactivity was also present in a hepatitis B immune globulin preparation, we are not aware of any similar documented adverse reaction to the latter preparation. Experiments analogous to these already outlined could similarly be performed with the hepatitis B immune globulin preparation to examine it for the presence of the same low-mol.-wt. substance.

We have described allergic generalized urticaria to the highly purified human anti-D immunoglobulin preparation. Despite the fact that adverse reactions to this preparation have been rare, a more purified product which might not contain the allergenic com-

ponent has been recently made available by the manufacturer. However, in conclusion, we would advocate extreme caution while deciding to give even the new preparation to anyone with proven allergy to the anti-D immune globulin preparation.

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