

A new strategy for the prevention of IgA anaphylactic transfusion reactions

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BACKGROUND: Management of patients with clinically significant anti-IgA is difficult and unsatisfactory in many aspects.

PATIENTS AND METHOD: A 40-year-old man with common variable immunodeficiency had a previous history of anaphylaxis after an intramuscular immunoglobulin administration. His serum contained anti-IgA, and he required immunoglobulins for recurrent infections.

RESULTS: The administration of intravenous immunoglobulins (IVIgG) containing less than 0.1 mg per mL IgA led to an anaphylactic reaction after the transfusion of only 2 to 3 mL. The same IVIgG charge was subsequently pretreated with freshly separated autologous plasma and given to the patient on three consecutive days without any reaction (1.25, 10, and 10 g each in 400 mL plasma). Anti-IgA activity did not increase, and the patient was treated again without complications.

DISCUSSION: Ex vivo pretreatment of IVIgG preparations with autologous plasma appears to be safe and useful in the management of patients with clinically significant anti-IgA. To achieve a significant IgA blockage, the preparation to be used should not contain large amounts of IgA.

CONCLUSION: The strategy described here appears to be safe and may help prevent anaphylaxis in many instances.

Anaphylaxis is a life-threatening response of sensitized individuals to a large number of different immunogens.¹ IgA anaphylactic transfusion reactions were first described in 1968² and have meanwhile been established by several investigators.³⁻¹¹ These rare events are estimated to occur in 1 of every 20,000 to 47,000 transfusions.^{7,12} IgA anaphylaxis can be prevented by using blood from donors completely lacking IgA and/or by thoroughly washing the blood cells to remove all donor IgA molecules.¹²⁻¹⁷ However, this is not always possible, and some patients may have to be treated with plasma derivatives containing variable concentrations of IgA.¹¹ Although some IVIgG have been used successfully in the management of predisposed patients,¹⁸ the risk of IgA anaphylaxis can not invariably be excluded. In fact, all commercially available IVIgG preparations are supplied with statements regarding the IgA content and contraindications in patients with anti-IgA and a history of anaphylaxis. In this study, we describe an effective and safe strategy for the prevention of IgA anaphylactic transfusion reactions.

MATERIAL AND METHODS

Concentrations of IgG, IgA, IgM, and circulating immune complexes were measured using rate nephelometry (Beckman Coulter, Krefeld, Germany) and ELISA (IMTEC Immundiagnostika, Berlin, Germany), respectively. The activity of anti-IgA was determined as described.¹⁹ Briefly, serial dilutions of serum samples (10 μ L in NaCl) were incubated with IgA-coated beads (human anti-IgA test card; DiaMed, Cressier sur Morat, Switzerland). After incubation for 5 minutes at room temperature, the ID-cards were centrifuged for 10 minutes and the results were read macroscopically. Positive reactions are demonstrated by agglutination of beads. Inhibition experiments were performed using serum preincubated (30 min at room temperature) with increasing amounts of IVIgG (Octagam, Octapharma).

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Received for publication September 25, 2003; revision received November 7, 2003, and accepted November 13, 2003.

TRANSFUSION 2004;44:509-511.

PATIENT AND RESULTS

The patient, a 40-year-old man with a known history of common variable immunodeficiency (IgG, 70.3; IgM, 18.6; and IgA < 6.7 mg/dL; reference ranges: IgG, 700-1600; IgM, 40-230; IgA 70-400 mg/dL), was suffering from recurrent infections and diarrhea. He was not receiving immunoglobulins because of the previous occurrence of anaphylaxis after an intramuscular immunoglobulin injection in 1970 (he could not remember the specific product). Using the newly developed particle agglutination test,¹⁹ we found that his serum contained a relatively strong anti-IgA (titer 1:32). Nevertheless, we decided to start IVIgG therapy using a preparation containing less than 0.1 mg per mL IgA (Octagam, Octapharma). After the infusion of roughly 2 to 3 mL, the patient developed serious reactions including pruritus, urticaria vomiting, and respiratory distress. The infusion was immediately stopped, and the patient was treated with an antihistamine, corticoid, and saline. On the next day, anti-IgA activity was still recognizable (titer 1:16), and in vitro experiments showed that the antibody in the patient's plasma is completely inhibitable, when 10 μ L of the used IVIgG were incubated with 180 μ L of patient's plasma. Based on this finding, 400 mL of the patient's plasma was apheresed using a cell separator (Haemonetics), then supplemented with 25 mL (1.25 g IgG) IVIgG. After 30 minutes of incubation at room temperature ($20 \pm 2^\circ\text{C}$), the mixture was transfused to the patient within 2 hours without any signs of incompatibility. This procedure was repeated on the 2nd and 3rd day using 10 g IVIgG in 400 mL of apheresed plasma. The patient felt absolutely well, and anti-IgA became undetectable after treatment. After 4 weeks, anti-IgA became detectable (titer 1:8), and the patient was treated with apheresed plasma and IVIgG (3×10 g each in 200 mL) without any complications (Fig. 1). Immune complexes containing IgG have been measured before and three times after treatment with IVIgG and, surprisingly, did not increase during observation. In contrast, IgG concentration increased adequately, and antibiotics were not required so far.

DISCUSSION

Anaphylactic transfusion reactions are rare but potentially dangerous events that are usually caused by anti-IgA.¹² They are less commonly induced by other plasma proteins, such as haptoglobin.²⁰ Until now, the only way to prevent IgA anaphylaxis was to use products completely lacking the causative antigen.^{12,21} However, such

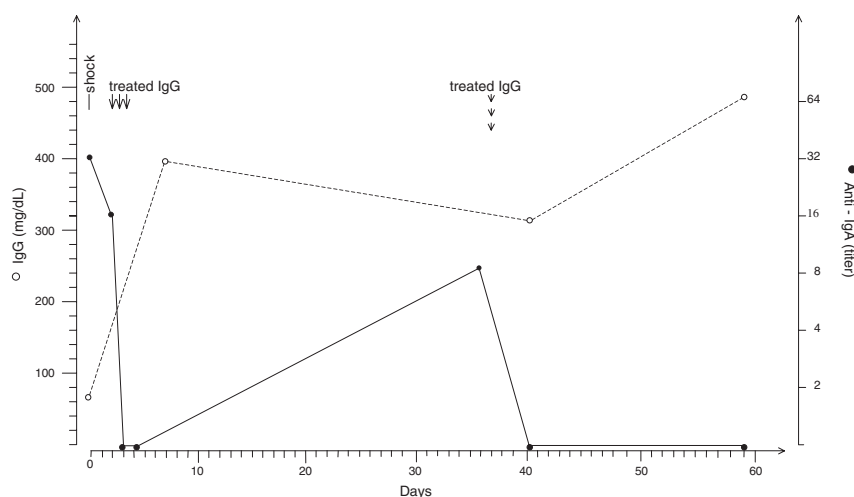


Fig. 1. Concentration of IgG and anti-IgA before and after treatment with IVIgG in apheresed autologous plasma.

products are not always available, and optimal treatment is not always possible. In this study, we describe a simple strategy for the prevention of IgA anaphylaxis. The IVIgG preparation that caused the reaction in our patient was ex vivo pretreated with autologous plasma, resulting in the compatibility of subsequent transfusions. We preferred the used IVIgG preparation because it contains only a small amount of IgA (<0.1 mg/mL) and because it is treated with SD. SD-treated plasma has been reported to be associated with fewer acute reactions than conventional plasma.^{22,23}

The described technique might be useful in the prevention of non-IgA-anaphylactic transfusion reactions as well. It may also be helpful in many other instances where the causative immunogens can be blocked without diminishing the effect of the therapeutic agent (i.e., anti-D prophylaxis and when vaccinating predisposed patients). In fact, during this study we successfully treated a second patient with pretreated IVIgG. This patient had previously developed anaphylactic reactions after intravenous and subcutaneous administration of different IVIgG preparations. The patient was suffering from autoimmune thrombocytopenia and isolated IgG deficiency, but the reason for the anaphylactic reactions remained unclear. The question whether this technique can also prevent IgE-mediated anaphylaxis remains a matter of speculation. It is also unclear whether a simple dilution of the causative antigens may play a role in certain cases.

Theoretically, ex vivo treatment of IVIgG preparations with autologous plasma can be effective in preventing anaphylactic reactions only if the number of the antibodies in the apheresed plasma is sufficient to block the causative immunogens completely or at least significantly. In the present case, we looked at how much IVIgG was required to inhibit the antibody in patient's plasma. We

found that roughly 400 mL of plasma was required for significant blockade of IgA molecules in 10 g IVIgG solution (<0.1 mg/mL according to the manufactures). It is obvious that not all IgA molecules were blocked by the ex vivo treatment because the anti-A became undetectable after treatment. Most importantly, the treatment did not result in an increase of circulating immune complexes. This suggests that very low concentrations of IgA may be tolerated by the affected patients. In fact, some IVIgG preparations have already been used successfully in the management of patients with clinically significant anti-IgA.¹⁸ These observations indicate that low doses of IgA-anti-IgA complexes formed by the new strategy in vitro or in vivo are clinically insignificant. However, harmful side effects cannot invariably be excluded. The question why anti-IgA did not rebound is obscure. This phenomenon has previously been described in other studies and cannot be explained yet.^{19,24}

In conclusion, the method described here appeared to be a safe and effective new strategy, not only for the prevention of IgA anaphylactic transfusion reactions in patients with clinically significant anti-IgA, but also for the prevention of severe allergic reactions in many similar cases.

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