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Routine intraoperative application of high-dose aprotinin in open heart surgery in adults: antibody formation after first exposure

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Summary

High-dose aprotinin is now routinely used in cardiac surgery to reduce post-operative blood loss and transfusion requirements, although several cases of anaphylactic reactions to the proteinase inhibitor have been reported. As part of a multi-centre study to evaluate the immunological response to aprotinin after first exposure 61 cardiac surgical patients were treated with the Hammersmith regimen. Patients with previous aprotinin exposure were excluded from the study. To determine specific IgG and IgE antibodies blood samples were taken pre-operatively, within 3 to 4 weeks and 6 to 7 months after operation. Determinations were made by using Western Blot and ELISA methods. Fifty-six patients were followed up for a 6-month period, 26 (46.4%) of them developed IgG antibodies to aprotinin determined by Western Blot, whereas only 14 (26.8%) patients with IgG antibodies were found by the ELISA. IgE antibodies were not found in any of the patients. On hospital admission and 6 months post-operatively additional intradermal prick tests were performed. No clear-cut positive reaction to the skin test was found in any patient.

Key words: Aprotinin – cardiac surgery– immunological responses – antibodies

Introduction

Aprotinin, a proteinase inhibitor, has been widely used in the treatment of various diseases such as pancreatitis and shock. At present its major indication is the reduction of post-operative blood loss and transfusion requirements in open heart surgery.^{5,6} Allergic reactions due to aprotinin are well known and have been reported in the literature.^{7,9} We participated in a multi-centre study to evaluate the immunological response to aprotinin ('Trasylol'[†]) after first exposure. IgG and IgE antibodies were determined by Western Blot and ELISA methods to reveal the extent of immunological response.

Patients and methods

Between October 1991 and February 1992, 61 adult patients (55 male, 6 female) underwent open heart surgery for coronary heart disease (80.3%) or acquired

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valvular heart disease (19.7%). The mean age was 58.5 ± 7.4 years. Hospital mortality was 6.5% (4 patients). One patient died four months after operation due to sudden cardiac arrest. With informed consent and institutional approval all patients received aprotinin according to the 'Hammersmith' regimen: 2 million KIU (Kallikrein Inactivator Units) were given as a loading dose at the beginning of surgery followed by 0.5 KIU/h during the operation.³ In addition, 2 million KIU were added to the priming solution. Aprotinin was supplied by Bayer AG (Germany) in bottles containing 200 ml of saline solution without any additives or preservatives, each containing 2 million KIU of aprotinin. Patients with a history of previous aprotinin exposure were not admitted to the study. The anaesthesia management, the operative procedure and the performance of cardiopulmonary bypass were standardized.

Biochemical analysis

On hospital admission, 3 to 4 weeks and 6 to 7 months after operation blood samples were taken to determine IgG and IgE antibodies by Western Blot and enzyme-linked immunosorbant assay (ELISA) methods. Aprotinin plasma levels were also determined, before surgery and 5 minutes after onset of cardiopulmonary bypass (CPB). Measurements were carried out by Bayer AG, Germany. Blood samples for routine blood tests (white blood cell count, red blood cell count, thrombocyte count, BUN, sodium and potassium plasma level, AST (SGOT) and ALT (SGPT) were obtained on admission, 5 minutes after onset of CPB, immediately after operation and on the third post-operative day.

Intradermal skin test

On admission and 6 months after operation a prick test was performed with aprotinin saline solution using a prick lancet. A positive reaction was defined as a wheal of at least 3 mm diameter surrounded by an erythema of at least 2 mm compared with a negative saline control. Smaller eruptions were judged as questionably positive. Patients with a positive or questionably positive outcome were tested a second time, 2 months later, with saline and histamine control.⁸

Results

IgG antibodies

Twenty-six out of 56 patients developed IgG antibodies to aprotinin. In 24 (96.4%) of them these were not detected until 6 months, whereas in 2 (3.6%) patients they were found only 3 weeks after operation. Interestingly, 66% of the female patients compared with 44% of the males revealed IgG antibodies. The less sensitive ELISA test gave positive results in 14 cases (26.8%). In one case the ELISA test showed a positive result while the Western Blot remained negative.

IgE antibodies

IgE antibodies to aprotinin could not be detected at either 3 to 4 weeks or 6 to 7 months post-operatively in any patient.

Intradermal skin test

No positive reaction was seen to the pre-operative prick test. Five patients developed a questionable or positive reaction after 6 to 7 months. Four of them also developed IgG antibodies while 1 remained negative. The control prick test performed 2 months later was unable to confirm these results.

Routine blood tests

All routine laboratory parameters were within the normal range.

Discussion

As aprotinin is a bovine protein there is a certain risk of sensitization. During the 40 years in which aprotinin has been on the German market a few allergic reactions have been reported.^{1,4,7,9} The majority of these reactions were seen during the second exposure to the drug.³ To evaluate the number of patients who may develop sensitization to aprotinin we studied the prevalence of specific IgG and IgE antibodies after first time exposure to the drug. In our series of 56 patients the incidence of IgG antibody development was 46.4% with the Western Blot method which was found to be more sensitive than the ELISA test. No IgE antibodies to aprotinin were detected during the 6-month follow-up. The significance and predictive value of the prick test cannot be assessed by this study: positive reactions in some patients could not be confirmed by a second test.

In order to evaluate the potential risk of allergic side-effects, further studies are required in patients receiving a second exposure to the drug.

Acknowledgement

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