Correspondence

Immunological Consequences of Topical Bovine Thrombin

To the Editor-in-Chief:

Topical bovine thrombin is commonly used for surgical hemostasis. In the 1980s, it was recognized that patients commonly made antibodies to bovine thrombin following exposure to these agents.^{1,2} These antibodies did not cross-react with human thrombin in most cases. However, it soon became apparent that the antibody responses to bovine thrombin could lead to immune responses to other plasma proteins and adverse clinical outcomes. In 1990, we reported a patient who developed antibodies to bovine thrombin and bovine factor V, with cross-reactivity to human factor V and life-threatening bleeding.³ Subsequently, other investigators documented the frequent occurrence of factor V inhibitors with bovine thrombin use in a variety of surgical settings.⁴

Recently, Ortel et al⁵ demonstrated, in a prospective series of 151 surgical patients, that more than 95% of patients developed antibodies to bovine thrombin or factor V and that approximately 50% of these patients had cross-reactivity to human coagulation factors. Adverse clinical outcomes were increased in patients exposed to bovine thrombin who had evidence of previous exposure to bovine thrombin preoperatively.

In a previous issue of *The American Journal of Pathology*, Schoenecker and colleagues⁶ report on the consequences of exposing mice to topical bovine thrombin. In addition to making antibodies to clotting factors, these mice made a variety of antibodies, such as anticardiolipin antibodies and antinuclear antibodies. Some mice developed antibody patterns and lesions consistent with a lupus-like syndrome. These data from mice demonstrate that use of bovine thrombin preparations may elicit a broader immunological response and physiological perturbation than previously reported.

Based on the available data, we suggest: 1) To better define the risk of autoimmune syndromes in humans following exposure to bovine thrombin, a prospective trial is

indicated to determine whether bovine thrombin use leads to the development of autoantibodies in patients, its prevalence, duration of antibody response, and correlation with clinical outcomes. 2) In the meantime, if needed, the purer preparation of bovine thrombin should be used, as it appears to be less immunogenic. As adverse clinical outcomes are associated with recurrent exposure to bovine thrombin, repetitive exposure to bovine thrombin should be avoided whenever possible.

Use of human thrombin would obviate the clinical problems associated with the use of a bovine protein preparation. Purified human thrombin from plasma donors could be considered, but carries with it some infectious risk. The ideal solution would be recombinant human thrombin and fibrinogen as replacement for the current forms of fibrin sealant. This would avoid potential prion-related or other infectious disease risk. However, the cost of this product is likely to be significantly higher.

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