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Antihuman Factor V Antibodies After Use of Relatively Pure Bovine Thrombin

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Although bovine thrombin is commonly used in the operating room, there is evidence that exposure to bovine thrombin can result in the development of autoimmune antibodies, usually against factor V, which can lead to a profound coagulopathy. It is thought that impurities in bovine thrombin preparations are responsible for the adverse reactions in patients. Here we describe a case in which exposure to a relatively pure bovine thrombin preparation resulted in the development of an antihuman factor V antibody-associated coagulopathy. This report calls into question the safety of even relatively pure bovine thrombin.

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Bovine thrombin preparations are the most widely used hemostatic agents in the United States. It is estimated that more than 500,000 patients per year are exposed to bovine thrombin [1]. Two preparations are currently in use: Thrombin-JMI (Jones Pharma, Inc, St. Louis, MO) is a relatively pure preparation, whereas Thrombogen (Johnson & Johnson, Arlington, TX) is a somewhat less pure preparation [2].

Several adverse events have been reported in association with the use of bovine thrombin [3-6]. Many of these case reports implicate antihuman factor V antibodies in the development of coagulopathy. These antibodies are thought to be elicited in response to exposure to bovine factor V, a contaminant present in bovine thrombin preparations. For this reason, the relatively pure preparation of bovine thrombin, Thrombin-JMI, is thought to be safer than the impure preparation, Thrombogen, although both continue to be used. Consistent with the idea that the pure form is safer, all of the observed complications reported thus far have followed exposure to Thrombogen. Conversely, Thrombin-JMI is currently a constituent in a variety of hemostatic agents.

A 74-year-old man was admitted to the hospital with worsening angina and dyspnea. Serum levels of cardiac

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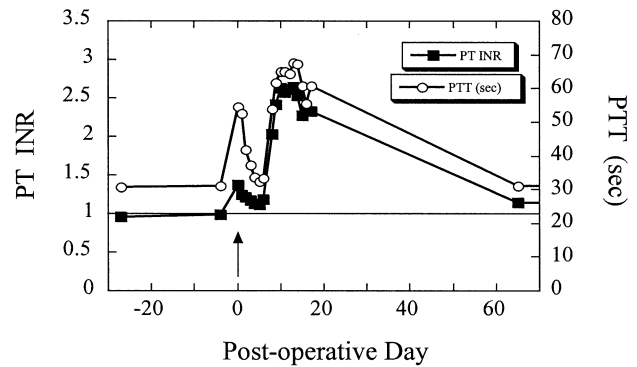


Fig 1. Abnormalities in prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT) after exposure to bovine thrombin.

enzymes were normal, and an electrocardiogram suggested no acute myocardial infarction. Cardiac catheterization revealed significant coronary disease, and an echocardiogram revealed normal left ventricular size, a left ventricular ejection fraction of 45%, and septal, inferior, and posterior wall hypokinesia. The patient was stabilized with medical management, discharged home, and coronary artery bypass grafting (CABG) was scheduled.

The patient's surgical history was significant for open cholecystectomy and umbilical hernia repair in 1982, coronary artery bypass grafting in 1983, lumbar laminectomy in 1991, and repair of an infrarenal abdominal aortic aneurysm in 2000. Further, from a review of the medical record, it was highly likely that the patient was exposed to a bovine thrombin preparation in at least one of the last three surgical procedures.

A five-vessel CABG was performed. The cross-clamp time was 86 minutes and the bypass time was 163 minutes. To achieve hemostasis, one FloSeal Matrix Hemostatic Sealant kit (Fusion Medical Technologies, Inc, Fremont, CA), which contains 5,000 U of Thrombin-JMI, was applied topically to the surgical wound at the time of closure. The patient was extubated on postoperative day 1, and the chest tubes and pacing wires were removed on day 2. On day 4, the patient's prothrombin time (PT) and partial thromboplastin time (PTT) were approximately normal. However, the PT and the PTT began to rise on day 7, and remained high for at least 10 days thereafter (Fig 1). The maximum PT international normalized ratio (INR) and PTT were 2.65 and 65.0 seconds, respectively. During this interval, no exogenous anticoagulants were administered, and no clinical bleeding events were noted. In part because of the unclear etiology of the patient's coagulopathy, his stay in the intensive care unit was extended during his hospitalization. The patient was discharged to home on postoperative day 18. At his return to the clinic on postoperative day 65, the PT and PTT had returned to normal (Fig 1).

An evaluation of plasma samples taken on postoperative day 12 revealed high levels of antibovine factor V_a immunoglobulin G (IgG) and antihuman factor V IgG (Fig 2). In addition, human factor V activity in the patient's plasma

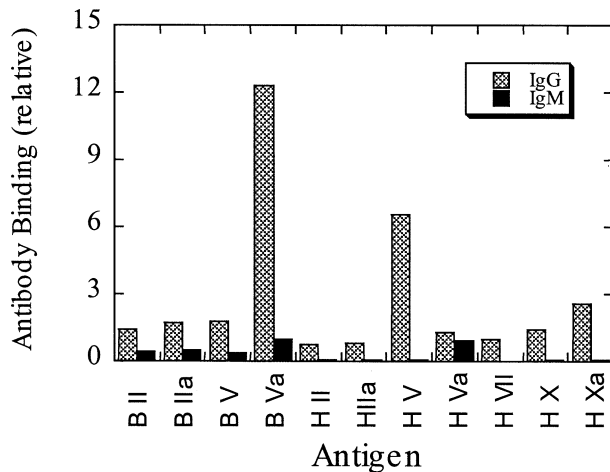


Fig 2. Antibodies against bovine (B) and human (H) coagulation factors after exposure to bovine thrombin as determined by enzyme-linked immunosorbent assay. Antibody binding is expressed as the fraction of binding found by using pooled normal human serum. Levels of immunoglobulin M (IgM) specific for human factor VII were not determined.

was low (9.2 activity units in the patient plasma compared with 79 to 133 activity units in normal plasma). This suggested that the antihuman factor V antibody may have resulted in some depletion of factor V, or may have inhibited factor V activity. The addition of exogenous human factor V (Haematech, Inc, Essex Junction, VT) to achieve normal levels in solution (7.0 µg/mL) resulted in *only partial* recovery of factor V activity, to 26 activity units. This suggests that the antihuman factor V at least partially blocked the function of the exogenous (and endogenous) factor V. Subsequent assays performed on postoperative day 149 revealed that the antifactor V IgG was absent from the patient's plasma, at which time the PT and PTT were normal (data not shown).

Comment

Several reports have pointed to bovine thrombin as a potential causative agent in the development of coagulopathies following surgical procedures [3-6], and this case similarly implicates antibodies against human factor V in the pathogenesis. However, we report that the antibodies were elicited following exposure to the relatively pure form of bovine thrombin, Thrombin-JMI. Like antibodies elicited by the impure form, these were specific for human factor V, were consistent with a secondary exposure, were IgG in nature, and appeared 1 week after exposure to the agent.

These findings call into question the mechanism(s) underlying the pathogenicity of complications that are associated with bovine thrombin. Thrombin itself is a highly immunostimulatory molecule and, even in the absence of impurities, may account for an adverse reaction given prior exposure to impure bovine thrombin. Consistent with this idea, studies in rodents indicate that pure bovine thrombin, although not as effective as the impure preparation, was immunostimulatory and could result in adverse humoral reactions [2]. On the other hand, even the relatively pure bovine thrombin preparation probably contains some level

of contaminants, and these contaminants may be involved in adverse immune reactions. The xenogeneic nature of the bovine thrombin may also be a contributing factor, although this remains unknown.

This report adds to a continuing body of evidence pointing to the dangers of bovine thrombin as a hemostatic agent and provides evidence in humans that the purified form of bovine thrombin may be dangerous. However, experience with the relatively pure form of bovine thrombin is still limited, and given the lack of alternatives in the United States, its continued use in life-threatening situations is still mandated. However, this report provides strong impetus for the testing of human plasma-derived thrombin products as an alternative to bovine products.

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Compression of Trachea and Left Main Bronchus by Arch Aneurysm

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We report on the case of a 70-year-old woman who presented dyspnea. Contrast-enhanced computed tomography of the chest revealed the compression of the lower part of the trachea and left main bronchus by an aneurysm of the ascending aorta and aortic arch. Although we performed a replacement of the ascending aorta and aortic arch, we were unable to relieve the stenosis of the trachea and bronchus. By the suspension of the posterior wall of the native aneurysm, we were able to successfully relieve the compression and alleviate the respiratory insufficiency.

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