

## CASE REPORTS

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## Normal Activated Clotting Time Despite Adequate Anticoagulation with Ancrod in a Patient with Heparin-associated Thrombocytopenia and Thrombosis Undergoing Cardiopulmonary Bypass

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ANCROD (Arvin, Knoll Pharmaceutical, Whippany, NJ), is a defibrinogenating enzyme purified from the venom of the Malayan pit viper (*Agkistrodon rhodostoma*). Ancrod has been proposed as an alternative to heparin for anticoagulation in patients with thromboembolic disorders and in patients with contraindications to heparin during cardiopulmonary bypass (CPB).<sup>1,2</sup> It is usually administered as a continuous infusion preoperatively and titrated to achieve plasma fibrinogen concentrations of 0.2-0.7 g/l to ensure adequate anticoagulation and to prevent thrombus in the extracorporeal circuit during CPB. The activated clotting time (ACT) is routinely used to ensure adequate

anticoagulation when heparin is used for anticoagulation for bypass.

Very little information has been published, however, on the optimal method for ensuring adequate anticoagulation in patients receiving ancrod for anticoagulation during CPB. In particular, the effect of ancrod-induced hypofibrinogenemia on the ACT has not been well characterized.<sup>1</sup> We describe a patient undergoing CPB with ancrod anticoagulation who, despite documented hypofibrinogenemia (0.33 g/l), maintained normal ACT values before CPB.

### Case Report

A 73-year-old man was referred to the University of Virginia Health Sciences Center for cardiac catheterization and possible coronary artery bypass grafting. His past medical history was significant for heparin-associated thrombocytopenia and thrombosis. In 1989 the patient had sustained a pelvic fracture, which was complicated by left leg deep vein thrombosis during hospitalization. After initiation of heparin therapy, he had developed thrombocytopenia and arterial thrombosis, resulting in ischemia of his left foot and requiring amputation of the lateral three toes.

The patient was admitted with unstable angina. Because of the history of heparin-associated thrombocytopenia and thrombosis, the patient was a candidate for the use of ancrod under a compassionate-use protocol approved by the Human Investigation Committee. An intravenous infusion of ancrod was begun, and the patient underwent cardiac catheterization without complication. The ancrod infusion was continued until the morning of surgery. One hour preoperatively, the fibrinogen concentration (0.35 g/l) was within the therapeutic range. The ancrod infusion was discontinued immediately before uneventful induction of anesthesia with sufentanil. Before cannulation

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for CPB, the results of four consecutive ACT samples were between 110 and 140 s (Hemochron celite-activated blood coagulation CA 510 test tubes, 12 mg Johns Manville celite, in a Hemochron 801 test unit, International Technidyne, Edison, NJ; normal range 100–140 s; therapeutic range for CPB > 400 s). At this time the fibrinogen concentration was 0.33 g/l.

Upon visual observation of whole blood a friable clot formed after approximately 2 min. The surgeon also reported loose thrombus formation in the surgical field. Although not part of the protocol, additional anecrod (0.25 U/kg) was infused over 30 min to prevent the potentially serious adverse effects of clot formation in the extracorporeal circuit. The ACT values during and immediately after the infusion remained normal, however, at 110 and 157 s, respectively. The fibrinogen concentration after the anecrod infusion was 0.18 g/l, and both the prothrombin time (PT) and activated partial thromboplastin time (aPTT) were greater than 200 s (normal ranges 10.4–12.6 and 24.8–37.2 s, respectively). Based on this information, CPB was instituted and no evidence of thrombus formation was noted in the extracorporeal circuit. The ACT after initiation of CPB was greater than 1,000 s. The patient's lowest temperature during bypass was 27°C. The preoperative and postoperative platelet counts were 169 and  $114 \times 10^9$  platelets/l, respectively (normal range  $150\text{--}450 \times 10^9$  platelets/l). There was no excess intraoperative blood loss.

After discontinuation of CPB, 2 U fresh frozen plasma and 5 U cryoprecipitate were administered. At the end of the operation the fibrinogen concentration after the administration of fresh frozen plasma and cryoprecipitate was 1.17 g/l. The PT, aPTT, and ACT were 18.2, 43.2, and 110 s, respectively.

The patient experienced no significant postoperative bleeding, and his trachea was extubated on the morning of the 1st postoperative day. There was no evidence of bleeding or coagulopathy or signs of perioperative thrombotic or embolic events.

## Discussion

Anecrod is an effective anticoagulant for the treatment of patients with thromboemboli.<sup>3</sup> In patients with contraindications to heparin, such as a history of heparin-associated thrombocytopenia with or without thrombosis or protamine allergy, anecrod provides a safe and effective alternative for treatment.<sup>2,4,5</sup> Some alternatives to standard heparin in patients undergoing CPB have been reported; however, none of these has been approved by the Food and Drug Administration for use in CPB. Apart from the strict avoidance of any further exposure to heparin, several experimental strategies are available to prevent the potentially hazardous recurrence of heparin-induced intravascular platelet aggregation and resultant arterial and venous thrombosis in patients with heparin-associated thrombocytopenia and thrombosis. One option is the preoperative treatment with aspirin and dipyridamole.<sup>6</sup> Investigational agents

either studied or possibly useful in this patient population include the prostacyclin analog ZK 36374 (iloprost),<sup>7</sup> low-molecular-weight heparins,<sup>8</sup> a heparinoid,<sup>9</sup> and specific thrombin inhibitors, such as argatroban<sup>10</sup> and hirudin.<sup>11</sup> The use of preoperative plasmapheresis also may be an option.<sup>12</sup> To our knowledge, no studies have been published comparing these alternatives in the treatment of thrombosis or prevention of thrombosis in the extracorporeal circuit in patients undergoing CPB.

Unlike thrombin, anecrod hydrolyzes only the A $\alpha$  chain of fibrinogen, cleaving off fibrinopeptide A but not fibrinopeptide B.<sup>13</sup> Importantly, anecrod is unable to perform other thrombin-mediated events, such as the activation of the procoagulant cofactors, factor V and factor VIII, and does not activate factor XIII, the enzyme responsible for cross-linking fibrin polymers into a stable clot.<sup>13,14</sup> Therefore, fibrin monomers formed by the action of anecrod aggregate to form a friable end-to-end linked polymer but cannot form a stable cross-linked lattice. Anecrod may also accelerate fibrinolysis by stimulating the release of tissue-type plasminogen activator from endothelial cells and by producing soluble fibrin, an important surface for the activation of plasminogen by tissue-type plasminogen activator.<sup>15</sup> The fibrin produced by the action of anecrod is rapidly degraded *in vivo*, leading to hypofibrinogenemia.<sup>14,15</sup> Anecrod-induced hypofibrinogenemia (0.2–0.7 g/l), while permitting adequate surgical hemostasis, does not allow spontaneous thrombus formation, thereby permitting the safe conduct of CPB. Friable, loose thrombus may form, however, and may result in ACT values within the normal range, as described in this case and observed by Zulys.<sup>||</sup>

The ACT value is determined by the addition of celite to whole blood, leading to clot formation *via* activation of the intrinsic coagulation pathway. The endpoint for clot formation may be either rapid gel formation or formation of fibrin strands. Polymers of fibrin produced by the action of anecrod may be able to form sufficient polymers to displace the rotating magnet in the ACT apparatus, signaling clot formation, and thus producing normal ACT values. By contrast, the PT and aPTT endpoints are detected by a photooptical clot-sensing system. Clot formation is detected by a rate of change in absorbance that exceeds a predetermined level over a defined time period. Moderate hypofibrinogenemia (fibrinogen concentration greater than 0.2 g/l) produced by the administration of anecrod may not produce a significant prolongation of the PT or aPTT.<sup>5</sup> In this case,

|| Zulys VY: Personal communication. 1993.

# Simon S: International Technidyne Corporation: Personal communication. 1993.

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despite normal ACT values, there was no evidence of thrombus formation in the CPB circuit, suggesting that the thrombus formed was unstable and clinically insignificant. We can only speculate on the precise cause or causes of the prolongation of the ACT, measured after initiation of CPB at greater than 1,000 s, but it is probably a multifactorial process. Potential contributors include hemodilution of fibrinogen, coagulation factors, and platelets in the pump circuit<sup>16,17,20</sup>; hypothermia<sup>17,21</sup>; instability of non-cross-linked fibrin polymer<sup>18</sup> to mechanical shear forces and turbulence encountered in the extracorporeal circuit<sup>19</sup>; and some degree of platelet dysfunction induced by CPB.<sup>19</sup>

When ancrod is administered for the treatment of deep venous thrombosis or retinal vein thrombosis before long-term oral anticoagulant therapy, such as with warfarin, ancrod is discontinued once the PT and international normalized ratio are in the therapeutic range. Reversal of the ancrod-induced hypofibrinogenemia with cryoprecipitate is usually not necessary. After major surgery involving CPB, however, blood product administration is often required, and in patients receiving ancrod, reversal of ancrod anticoagulation may be necessary if undue bleeding is encountered. Infusion of cryoprecipitate, as a source of fibrinogen, is sufficient to reverse the effects of ancrod.

In conclusion, we report a case of adequate anticoagulation for CPB with ancrod despite normal ACT values. Measurement of fibrinogen concentrations before, during, and after CPB may be the only effective way to monitor ancrod-induced anticoagulation.

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