Drotrecogin alpha and anticoagulants in septic patients after cardiac surgery

doi: 10.1017/S0265021506001657

EDITOR:

Drotrecogin alpha (Xigris®; Eli Lilly and Company, IN, USA) is a recombinant form of human activated protein C (Fig. 1). It was approved by the Food and Drug Administration in 2001 for the treatment of severe sepsis in adult patients who are at high risk of death [1].

The protein C worldwide evaluation in severe sepsis (PROWESS) trial [2] details that drotrecogin alpha (activated) should be given to patients with septic shock, acute physiology and chronic health evaluation (APACHE) II >24 and at least one new (<48 h) organ dysfunction, provided there is no risk of bleeding. The absence of a beneficial treatment effect, coupled with an increased incidence of serious bleeding complications, indicates that it should not be used in patients with severe sepsis who are at low risk of death, such as those with single-organ failure or an APACHE II score less than 25.

In the recombinant human activated PROWESS study, patients at an increased risk of bleeding were excluded. Nevertheless, the incidence of bleeding with drotrecogin alpha was 3.5% vs. 2% for placebo ($P = 0.06$), and these events occurred primarily during the infusion period (2.4% vs. 1%; $P = 0.02$). The incidence of serious bleeding was similar for those who received drotrecogin alpha alone and those who also received prophylactic heparin (3.5% vs. 3.7%); however, patients at higher risk of bleeding or with a lower platelet count were less likely to receive heparin prophylaxis.

Significant interactions have been noted [3] between heparin and activated protein C promoting bleeding and recommendations have been made to avoid the administration of anticoagulants during the infusion of drotrecogin alpha. These recommendations make it hard to be used in cardiac surgery especially in patients with prosthetic mechanical heart valves or atrial fibrillation. We describe two patients who underwent open-heart surgery and received drotrecogin alpha (activated) for postoperative sepsis.

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Accepted for publication 31 July 2006
First published online 23 October 2006 EJA 4082

Patient 1

A 56-yr-old male with Marfan's syndrome underwent reoperative cardiac surgery for aortic regurgitation, ascending aorta aneurysm and malfunction of a mechanical prosthetic mitral valve which had been implanted 8 yr earlier. He had a severe kyphoscoliotic deformity of the thorax with chronic restrictive respiratory disease. He underwent combined aortic valve graft replacement and removal of deposits on the mitral valve. Intraoperative and early postoperative course were uneventful and the patient was extubated on postoperative day 1. On day 5 the patient developed fever, leucocytosis and respiratory failure and required intubation and mechanical ventilation with F_iO_2 0.8 and positive end-expiratory pressure (PEEP) 8 cm H_2O. A presumptive diagnosis of pneumonia was made and vancomycin, levofloxacine and ceftazidime were started. The next day the patient was started on vasopressors for haemodynamic instability and showed signs of renal dysfunction (creatinine 2.1 mg dL^{-1} and oliguria). By that time the patient was taking warfarin, with an international normalized ratio (INR) >2, and unfractionated heparin. The platelet count was 164×10^9 L^{-1}. Drotrecogin alpha (24 μg kg^{-1} h^{-1} for 96 h) was started and heparin and warfarin were stopped. The first day thereafter pressors were stopped and F_iO_2 decreased to 0.6. Sputum culture was positive for *Escherichia coli*. At the end of the treatment the patient was haemodynamically stable, with normal renal function, and the patient was weaned from mechan-

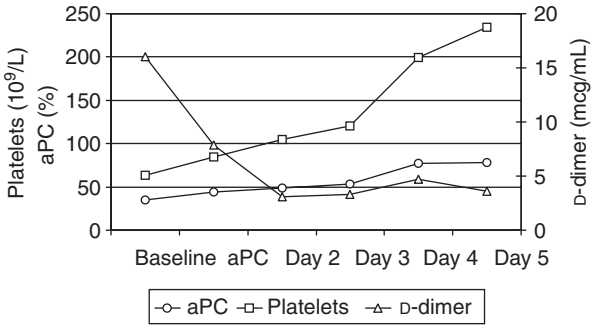

Figure 1.
Clinical course of biological parameters during treatment with activated protein C2.

ical ventilation. The INR was 1.9 and the platelet count was $223 \times 10^9\,L^{-1}$. There were no signs of bleeding or of prosthetic valve thrombosis, and warfarin was restarted. The patient was discharged from the ICU on day 21 and is alive at follow-up.

Patient 2

A 76-year-old female, with insulin-dependent diabetes mellitus and mild renal failure, underwent mitral valve repair, coronary artery bypass grafting and radiofrequency ablation for chronic atrial fibrillation. The early postoperative course was characterized by low cardiac output syndrome secondary to right ventricular failure, which necessitated mechanical ventilation and inotropic support. On day 5 the patient developed fever (38°C) and leucocytosis. Pressors were started and oliguria ensued (creatinine raised to $3.68\,mg\,dL^{-1}$). The patient also had acidosis and a low platelet count ($85 \times 10^9\,L^{-1}$; INR 1.27).

Drotrecogin alpha was started at $24\,\mu g\,kg^{-1}\,h^{-1}$ for 96 h and heparin was maintained at $800\,IU\,h^{-1}$. The time course of the biochemical parameters during treatment is shown in Figure 1. At the end of the first 48 h inotropes were tapered off, sedation was stopped and a diuresis developed. Blood cultures were positive for methicillin resistant *Staphylococcus aureus*. Twelve hours after the end of the infusion the patient underwent percutaneous tracheostomy without any bleeding complication. No major adverse event was recorded and the patient is alive at 30 days follow-up.

No data are available, to our knowledge, on patients submitted to mechanical heart-valve replacement and who develop postoperative sepsis and eventually receive therapy with drotrecogin alpha (activated). Indeed, the translation of successful clinical trials of this drug into prescribing indications is extremely difficult in the cardiac surgery context: these patients might have an extremely high risk of bleeding due to the concomitant need for systemic anticoagulation and the pharmacological effects of the drug. Moreover, the definition of sepsis with organ failure in the early postoperative course after cardiac surgery is still to be determined.

Because of its anticoagulant properties, the use of drotrecogin alpha (activated) is associated with an increased incidence of bleeding, which might be extremely high if concomitant therapeutic doses of anticoagulants are administered. The interactions between anticoagulants and endogenous peptides are complex and it might be speculated that, as heparin causes a deficit in the synthesis of thrombin, it plays a role as a co-factor of morbidity in patients with a debit of activated protein C secondary to sepsis.

In septic patients treated with therapeutic doses of unfractionated heparin, the conversion of protein C to its activated form may be impaired not only as a result of the sepsis-induced downregulation of thrombomodulin but also by the reduced generation of thrombin due to the effects of heparin. On the other hand, the inflammatory, procoagulant and antifibrinolitic response of sepsis induced by thrombin might be blunted by the simultaneous treatment with unfractionated heparin.

In patient 2, the rise in D-dimer levels after the completion of the 96-h infusion of drotrecogin alpha might indicate incomplete resolution of the procoagulant state seen in patients with sepsis. Indeed, despite heparin administration, the sepsis-mediated procoagulant state via thrombin generation is strongly activated and can be effectively halted.

In addition to these pathophysiological issues, there is a large gap in coagulation monitoring at the bedside during treatment: routine coagulation parameters may help in identifying patients at higher risk of bleeding, but is not indicated to adjust drug dosage. Further studies for the development of appropriate monitoring of interactions between anticoagulants and activated protein C are warranted.

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https://doi.org/10.1017/S0265021506001657 Published online by Cambridge University Press