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CASE REPORT

Human protein C concentrate in a patient with meningitis and bleeding as a complication of treatment with recombinant activated protein C

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ABSTRACT

Some case reports suggest that protein C zymogen supplementation may improve the outcome of patients with congenital or acquired protein C deficiency, such as sepsis-induced purpura fulminans. We describe the case report of a patient suffering from meningitis who developed a bleeding complication after recombinant human activated protein C administration and was successfully treated without any further bleeding complication with protein C concentrate.
Protein C concentrate can be considered in adult patients with meningitis, even if at risk or in the presence of bleeding.

Key words: sepsis, purpura fulminans, protein C, bleeding

Introduction

Because of the significant reduction in all-cause mortality, (1) recombinant human activated protein C (rhAPC, Xigris, Lilly) was approved for the treatment of adult patients with severe sepsis, at a high risk of death (typically APACHE II > 25 or multiple organ failure) and with a low-moderate risk of bleeding. (2) In 2012 however, Lilly withdrew rhAPC from the market following the negative results of the Prowess-Shock study. (3)

Protein C zymogen concentrate (PCc, Ceprotin, Baxter) may improve the outcome of patients with acquired PC deficiency and has been used in children, (4,5) and less frequently, in adult patients. (6,7)

With ethical committee authorization we describe the case report of a patient with meningitis who developed a bleeding complication during rhAPC administration and was successfully treated with PCc without any further bleeding complications.

Case presentation

A 45 year old patient was admitted to the intensive care unit (ICU) of our teaching hospital five hours after presenting to the emergency department with meningitis, as documented by coma (Glasgow coma scale = 8), pyrexia, rigor nucalis, petechiae and severe sepsis with hypotension, oliguria, acidosis, dyspnea requiring mechanical ventilation, high serum creatinine (2,2 mg/dL) and C reactive protein (150 mg/L). Computer tomography of the brain was normal and liquor analysis revealed proteins and nucleate cells.

Broad spectrum antibiotic was started (ceftriaxone, ampicillin and acyclovir) in association with dexamethasone. In spite of aggressive medical therapy, (1) intense fluid resuscitation, and increasing doses of norepinephrine up to 1.5 μg/kg/min, the patient developed progressive worsening of tissue perfusion with multiple organ failure (anuria, hypotension, hypoxia, acidosis and a platelet count of 45 x 10^9/L).

Eight hours after admission to the ICU, the patient was in a life-threatening situation with multiple organ failure and an APACHE II score of 30. He received activated protein C (Xigris) at standard doses (24 μg/kg/h) and vancomicin was added to the antibiotic therapy.

Xigris was interrupted after 30 hours of continuous infusion because of worsening petechiae and profuse bleeding from the mouth and from arterial and venous lines insertion sites. The platelet count was 10 x 10^9/L and platelet

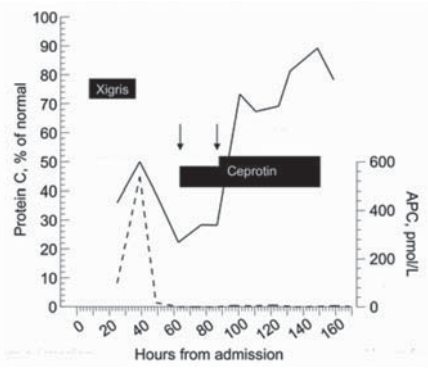

Figure 1. Variation of protein C level during drug administration.

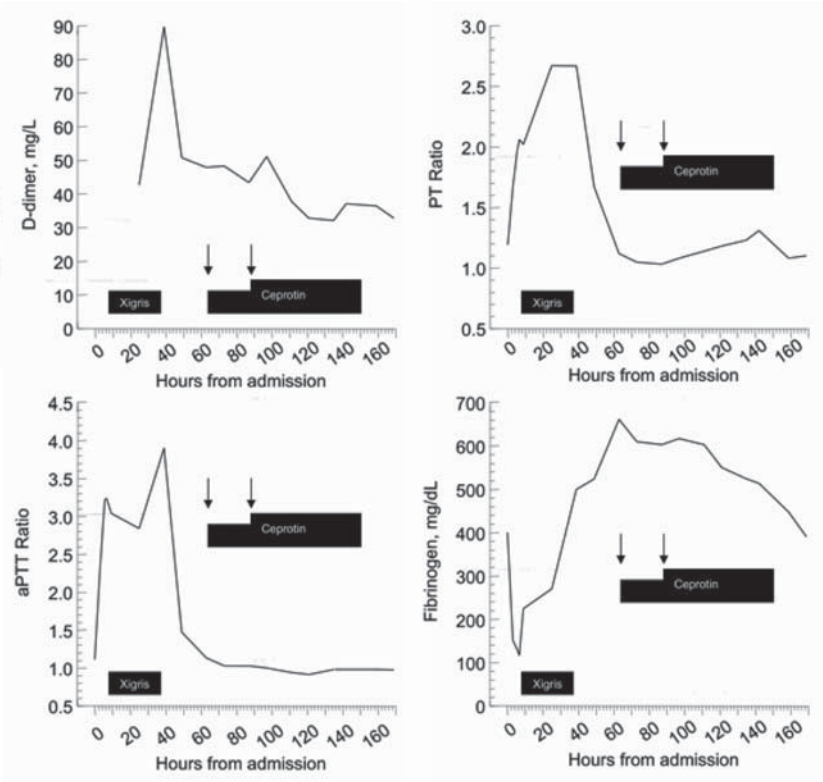

Figure 2. Variation of coagulation parameters during protein C administration.

concentrates were administered. Although the patient had apparently attained hemodynamic stability (norepinephrine was suspended), he was still in a life threatening situation with multiple and worsening organ failure. In view of the platelet count (17 x 10^9/L), protein C plasma levels (20% of normal) and previous bleeding complications, it was decided to start PCc (Ceprotin); a 6000 IU bolus was followed by a continuous infusion of 200 IU/h. Twenty-four hours later, protein C was still 35% of normal; a 6000 IU PCc bolus was again administered and the continuous infusion rate increased to 300 IU/h for 62 hours, attaining a protein C level of 90% at the end of the infusion (figure 1). Figure 2 shows Prothrombine Time (PT), Activated Partial Thromboplastin Time (aPTT), D-Dimer and fibrinogene levels during the study drug infusion.

Liquor and blood cultures were negative. The patient was discharged from ICU 10 days later and at 30 days was an outpatient at the nephrology department because of severe renal failure requiring dialysis once a week.

Discussion

This is the first case report that describe the use of PCc after a bleeding complication of rhAPC. If the role of PCc in adult patients was previously limited to patients with bleeding contraindications to rhAPC, it is possible that, after withdrawal of rhAPC from the market, PCc will be used more.

Protein C is a serine protease vitamin K dependent zymogen with antithrombotic, antinflammatory and profibrinolytic properties. During severe sepsis there is a reduction in PC concentration. PC deficiency leads to increased activation of the coagulation system, resulting in thrombin generation and, eventually, intravascular clot formation with thrombosis. (8) Numerous studies have demonstrated that decreased circulating levels of PC in septic patients are associated with increased morbidity and mortality. (9)

PCc is presently utilized as a therapy for patients with congenital deficiency of PC and for purpura fulminans treatment. In these patients with a high risk of bleeding, PCc administration seems to be a useful alternative to the activated form (rhAPC). Nonetheless, in order to recommend the use of PCc in the management of severe sepsis and septic shock it would be necessary to confirm these encouraging findings with a randomised multicenter controlled trial.

Updating a systematic search of the literature (10) to identify all the PCc administrations in adult septic patients, we found only 10 papers in the scientific literature (11 with the present case report) accounting for overall less than 90 patients.

The largest study, reported by Baratto et al., (6) described the efficacy and safety of PCc for restoring physiological values in 20 adult septic patients having clinical contraindications to treatment with rhAPC. They found a significant improvement of clinical and coagulation parameters. They observed a mortality of 35% while the predicted mortality based on SAPS II (55.1±13.2) was 58.9%.

The only randomized study on PCc ever published is a dose finding study in a pediatric population that was not powered to show an effect on mortality rate but did show a positive effect on sepsis induced coagulation disturbances. (5)

We conclude that PCc can be considered in patients with meningitis, even if at risk or in the presence of bleeding. The recent withdrawal from the market of rhAPC will probably slightly increase its field of application, including adult patients.

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